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(71) Applicant: THE DU PONT MERCK PHARMACEUTICAL COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

(72) Inventors: AMPARO, Eugene, Cruz; 107 Garfield Avenue, West Chester, PA 19380 (US). MILLER, William, Henry; 1909 Coventry Lane, Glen Mills, PA 19342 (US). PACOFSKY, Gregory, James; 86A Paladin Drive, Wilmington, DE 19802-1715 (US). WITYAK, John; 127 Kelton Road, West Grove, PA 19390 (US).

(74) Agents: REINERT, Norbert, F. et al.; The Du Pont Merck Pharmaceutical Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

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(54) Title: BORONIC ACID AND ESTER INHIBITORS OF THROMBIN

(57) Abstract

Novel boronic acid derivatives of formula (I), which are useful inhibitors of trypsin-like enzymes, are disclosed: R^1-Z-CHR^2-BY^1Y^2.

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Title

Boronic Acid and Ester Inhibitors of Thrombin

Field of the Invention

This invention relates to the discovery of new boronic acid derivatives which are inhibitors of thrombin and pharmaceutical compositions thereof.

Background of the Invention

Hemostasis is the normal physiological process in which bleeding from an injured blood vessel is arrested. It is a dynamic and complex process in which thrombin plays a key role. Blood coagulation may occur through either of two cascades of zymogen activations, the extrinsic and intrinsic pathways of the coagulation cascade. The last protease in each pathway is thrombin, which acts to hydrolyze four small peptides (two FpA and two FpB) from each molecule of fibrinogen, thus deprotecting its polymerization sites. Once formed, the linear fibrin polymers may be cross-linked by factor XIIIa, which is itself activated by thrombin. In addition, thrombin is a potent activator of platelets, upon which it acts at specific receptors. Thrombin activation of platelets leads to aggregation of the cells and secretion of additional factors that further accelerate the creation of a hemostatic plug. Thrombin also potentiates its own production by the activation of factors V and VIII (see Hemker and Beguin in: Jolles, et. al., "Biology and Pathology of Platelet Vessel Wall Interactions," pp. 219-26 (1986), Crawford and Scrutton in: Bloom and Thomas, "Haemostasis and Thrombosis," pp. .47-77, (1987), Bevers, et. al., *Eur. J. Biochem.* **1982**, *122*, 429-36, Mann, *Trends Biochem. Sci.* **1987**, *12*, 229-33).

Thrombosis may be regarded as the pathological condition wherein improper activity of the hemostatic

mechanism results in intravascular thrombus formation. Etiological factors such as the presence of atherosclerotic plaque, phlebitis and septicemia may cause thrombosis, leading to impaired blood flow to the effected tissues and possible serious pathological consequences.

Currently, two of the most effective classes of drugs in clinical use as anticoagulants are the heparins and the vitamin K antagonists. The heparins are ill-defined mixtures of sulfated polysaccharides that bind to, and thus potentiate the action of antithrombin III. Antithrombin III is a naturally occurring inhibitor of the activated clotting factors IXa, Xa, XIa, thrombin and probably XIIa (see Jaques, *Pharmacol. Rev.* **1980**, *31*, pp. 99-166). The vitamin K antagonists, of which warfarin is the most well-known example, act indirectly by inhibiting the post-ribosomal carboxylations of the vitamin K dependent coagulation factors II, VII, IX and X (see Hirsch, *Semin. Thromb. Hemostasis* **1986**, *12*, 1-11). While effective therapies for the treatment of thrombosis, heparins and vitamin K antagonists have the unfortunate side effects of bleeding and marked interpatient variability, resulting in a small and unpredictable therapeutic safety margin. The use of direct acting thrombin inhibitors is expected to alleviate these problems.

Thrombin is a serine protease having trypsin-like specificity for the cleavage of sequence-specific Arg-Xxx peptide bonds. As with other serine proteases, the cleavage event begins with an attack of the active site serine on the scissile bond of the substrate, resulting in the formation of a tetrahedral intermediate. This is followed by collapse of the tetrahedral intermediate to form an acyl enzyme and release of the amino terminus of the cleaved sequence. Hydrolysis of the acyl enzyme then releases the carboxy terminus.

A number of naturally occurring thrombin inhibitors have been reported. These include nazumamide A from *Theonella sp.* (see Fusetani, et. al., *Tetrahedron Lett.* **1991**, *32*, 7073-4), cyclotheonamide A from *Theonella sp.* (see Fusetani, et. al., *J. Am. Chem. Soc.* **1990**, *112*, 7053-4), amblyommin from *Amblyomma hebraeum* (see Bonin, et. al., EP 345614), hirudin from *Hirudo medicinalis*, recombinant versions of hirudin and hirudin fragments (see Rigbl and Jackson, EP 352903, Koerwer, WO 9109946, Meyer, et. al., WO 9108233, Dawson, et. al., WO 9109125, Maraganore, et. al., WO 9102750 and Maraganore, EP 333356).

Synthetic thrombin inhibitors have also been disclosed. Arylsulfonylarginine amides such as (2*R*,4*R*)-4-methyl-1-[N^2-{(3-methyl-1,2,3,4-tetrahydro-8-quinolinyl)sulfonyl}-*L*-arginyl]-2-piperidinecarboxylate have been shown to be effective inhibitors of thrombin (see Okamoto, et. al. *Thromb Res.* **1976**, *8*, 77-82, Ohshiro, et. al., *Blood Vessel* **1983**, *14*, 216-8), as have compounds containing constrained arginine mimics such as (2-naphthylsulfonylglycyl)-4-amidino-phenylalanyl piperidide (see Stuerzebecher, et. al., *Thromb. Res.* **1983**, *29*, 635-42), 1-[2-[5-(dimethylamino)naphth-1-ylsulfonamido]-3-(2-iminohexahydropyrimidin-5-yl)propanoyl]-4-methylpiperidine dihydrochloride (see Ishikawa, JP 88227572 and Ishikawa and Inamura, JP 88227573), *N*-(*trans*-4-amino-methylcyclohexylcarbonyl)-4-*O*-(2-picolyl)-*L*-tyrosine 4-acetanilide dihydrochloride (see Okamoto, et. al., EP 217286) and 4-[(aminoiminomethyl)amino]benzoic acid esters (see Fuji, et. al., DE 3005580, Matsuoka, et. al., *Jpn. J. Pharmacol.* **1989**, *51*, 455-63, and Takeshita, et. al., EP 435235).

Inhibitor design has benefitted from the knowledge of the mechanism of action and of the peptide sequences

which are thought to bind in the catalytic site of thrombin, e.g., -Gly-Val-Arg-Gly- of fibrinogen (see Blombäck, et. al., *J. Biol. Chem.*, **1972**, *247*, 1496-512), Ile-Pro-Arg-Ser- of prothrombin (see Magnussen, et. al., in: Reich, et. al., "Proteases and Biological Control," pp. 123-149 (1975)) and -Val-Pro-Arg-Gly- of factor XIII (see Takagi and Doolittle, *Biochemistry* **1974**, *13*, 750-6 and Nakamura, et. al., *Biochem. Biophys. Res. Commun.* **1974**, *58*, 250-256). This class of mechanism-based inhibitors are exemplified by the tripeptide aldehyde *D*-Phe-Pro-*N*-Me-Arg-H (see Bajusz, et. al., *J. Med. Chem.* **1990**, *33*, 1729-35), the chloromethyl ketone Ac-(*D*)-Phe-Pro-ArgCH$_2$Cl (see Kettner and Shaw, *Thromb. Res.* **1979**, *14*, 969-73) and the trifluoromethyl ketone *D*-Phe-Pro-ArgCF$_3$ (see Kolb, et. al., US 697987).

Kettner and Shenvi (EP 293881, published June 12, 1988), disclose peptide boronic acid inhibitors of trypsin-like proteases of formula (1)

$$R^1\text{-}[(A^3)_q(A^2)_p(A^1)_o]_n\text{-NH-CHR}^2\text{-BY}^1Y^2 \qquad (1)$$

wherein Y^1 and Y^2, independently, are hydroxyl or fluoro or, taken together, form a moiety derived from a dihydroxy compound having at least two hydroxy groups separated by at least two connecting atoms in a chain or ring, said chain or ring comprising 1 to about 20 carbon atoms and, optionally, a heteroatom which can be N, S, or O; R^2 is a substituted alkyl selected from the group consisting of $-(CH_2)_z-X$, $-CH(CH_3)-(CH_2)_2-X$, $-CH_2-CH(CH_3)-CH_2-X$, $-(CH_2)_2-CH(CH_3)-X$ and $-(CH_2)_2-CH(CH_3)-X$, where X is $-NH_2$, $-NH-C(NH)-NH_2$ or $-S-C(NH)-NH_2$, and z is 3 to 5; n, o, p and q are, independently, either 0 or 1; A^1, A^2 and A^3 are, independently, amino acids of *L*- or *D*-configuration selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val; and R^1

is a peptide comprised of 1 to about 20 amino acids, an acyl or a sulfonyl group comprised of 1 to about 20 carbon atoms, H, or an N-terminal protecting group. In this disclosure, Kettner and Shenvi demonstrated that the pinanediol esters of boropeptides are pharmacologically equivalent to the corresponding boronic acids.

Metternich (EP 0471651 A2) discloses borolysine thrombin inhibitors of formula (2)

$$W\text{-}Y\text{-}NR^4\text{-}CHR^5\text{-}BQ^1Q^2 \quad (2)$$

wherein W is an N-protecting group; Y is a sequence of n amino acids such that the n+1 amino acid peptide Y-Lys or Y-Arg has an affinity for the active site of a trypsin-like protease; where n is an integer of from 1 to 10 and in which at least one amino acid is an unnatural amino acid having a hydrophobic side chain; Q^1 and Q^2 are the same or different and are selected from $-OH$, $-COR_1$, $-CONR_1R_2$, $-NR_1R_2$ or $-OR_3$ of Q^1 and Q^2 taken together form a diol residue; R_1, R_2 and R_3 which may be the same or different, are C_{1-10}alkyl, C_{6-10}aryl, C_{6-10}aralkyl, or phenyl substituted by up to three groups selected from C_{1-4}alkyl, halogen and C_{1-4}alkoxy; R_4 is hydrogen or C_{1-10}alkyl; R_5 is a group -A-X; wherein A is $-(CH_2)_z-$ in which z is 2, 3, 4 or 5; $-CH(CH_3)-(CH_2)_2-$; $-CH_2-CH(CH_3)-CH_2-$; $-(CH_2)_2-CH(CH_3)-$; $-(CH_2)_2-C(CH_3)_2-$; $CH(CH_3)-(CH_2)_3-$; $-CH_2-CH(CH_3)-(CH_2)_2-$; $-CH_2-CH_2-CH(CH_3)-CH_2-$; $-(CH_2)_3-CH(CH_3)-$; $-(CH_2)_3-C(CH_3)_2$: C_{6-10}aryl C_{6-10}aralkyl and X is $-NH_2$, $-NH-C(NH)-NH_2$, $-S-C(NH)-NH_2$, $-N_3$, $-C_{1-4}$alkoxy, C_{1-4}alkylthio or $Si(CH_3)_3$ or R_4 and R_5 taken together form a trimethylene group and the asymmetric carbon atom may have the D- or L-configuration or represent any mixture of these.

Surprising for their lack of a basic residue at P_1 are tripeptide thrombin inhibitors comprised of 1-

aminoboronic and 1-aminophosphonic acid analogs of 3-methoxy-propylglycine (see Claeson, et. al., US 07-245428) and pentylglycine (see Cheng, et. al., "Symposium on Thrombosis and Hemostasis," 1991, Amsterdam, Abstract 2150).

In addition to thrombin inhibition, boropeptides have been disclosed with utility as a treatment for tumors, viral infections and arthritis (US 4963655A and EP 354522A), emphysema (US 4499082A), hypertension (EP 315574A) and as factor VII/VIIa inhibitors (WO 8909612A). Kleemann, et. al. (AU A-24693/88) disclose renin-inhibiting 1-amino boronic acid derivatives of formula (3)

$$A^1\text{-}A^2\text{-}HN\text{-}CHR^2\text{-}BXR^3(YR^4) \qquad (3)$$

in which A^1 denotes a radical of formulae (4-8).

$$R^1NR^6\text{-}CHR^5\text{-}CO\text{-} \qquad (4)$$
$$R^1CHR^{12}\text{-}CHR^5\text{-}CO\text{-} \qquad (5)$$
$$R^1NR^6\text{-}CHR^5\text{-}CHR^7\text{-}CHR^8\text{-}CHR^9\text{-}CO\text{-} \qquad (6)$$
$$R^1CHR^{12}\text{-}CHR^5\text{-}CHR^7\text{-}CHR^8\text{-}CHR^9\text{-}CO\text{-} \qquad (7)$$
$$R^{10}\text{-}(CH_2)_n\text{-}CH(CH_2)_mR^{11}\text{-}CO\text{-} \qquad (8)$$

Despite the foregoing, more efficacious and specific thrombin inhibitors are needed as potentially valuable therapeutic agents for the treatment of thrombosis. None of the cited references describe or suggest the new thrombin-inhibiting boronic acid derivatives of the present invention.

Summary of Invention

The present invention pertains to novel compounds of formula (I):

$$R^1\text{-}Z\text{-}CHR^2\text{-}BY^1Y^2$$
(I)

wherein

Y^1 and Y^2 are independently

a) -OH,

b) -F,

c) $-NR^3R^4$, or

d) C1-C8-alkoxy;

Y^1 and Y^2 when taken together can form

a) a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, a heteroatom which can be N, S, or O,

b) a divalent cyclic boro amide where said chain or ring contains from 2 to 20 carbon atoms,

c) a cyclic boro amide-ester where said chain or ring contains from 2 to 20 carbon atoms;

Z is

a) $-(CH_2)_mCONR^8-$,

b) $-(CH_2)_mCSNR^8-$,

c) $-(CH_2)_mSO_2NR^8-$,

d) $-(CH_2)_mCO_2-$,

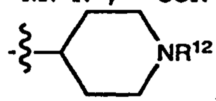
e) $-(CH_2)_mC(S)O-$, or

f) $-(CH_2)_mSO_2O-$;

R^1 is

a) $-(CH_2)_p$-aryl, wherein aryl is phenyl, naphthyl or biphenyl substituted with one, two or three substituents selected from the group consisting of halo (F, Cl, Br, I), -CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, methylenedioxy, $-R^8$, $-OR^8$, $-NO_2$, $-CF_3$, $-S(O)_rR^7$,

$-NR^8R^9$, $-COR^8$, $-CO_2R^8$, $-CONR^8R^9$, NR^8COR^9;



;

b) heteroaryl, wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted:

i) 5- or 6-membered aromatic ring, which contains from 1 to 3 heteroatoms selected from the group consisting of O, N, and S,

ii) quinolinyl,

iii) isoquinolinyl,

iv) benzopyranyl,

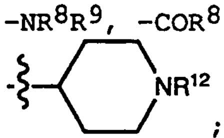
v) benzothiophenyl,

vi) benzofuranyl,

vii) 5,6,7,8-tetrahydroquinolinyl

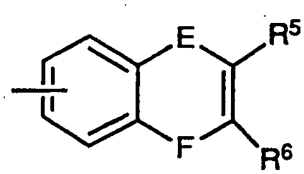
viii) 5,6,7,8-tetrahydroisoquinolinyl

and wherein the substituents are members selected from the group consisting of halo (F, Cl, Br, I), -CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, $-R^8$, $-OR^8$, $-NO_2$, $-CF_3$, $-S(O)_rR^7$, $-NR^8R^9$, $-COR^8$, $-CO_2R^8$, $-CONR^8R^9$, NR^8COR^9, $NRCO_2R^9$,



;

c)



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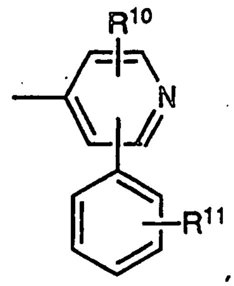

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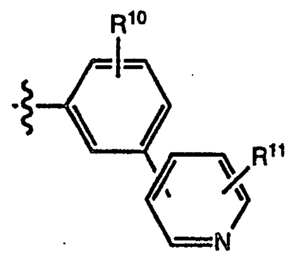

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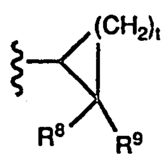
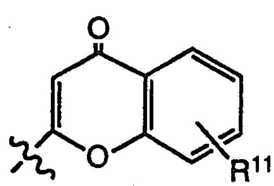


g) 

R^2 is

a) $-(CH_2)_n-NHC(NH)NH_2$,

b) $-(CH_2)_n-NHC(NH)NHCOCH_3$,

c) $-(CH_2)_n-SC(NH)NH_2$,

d) $-(CH_2)_n-SC(NH)NHCOCH_3$,

e) $-(CH_2)_n-NH_2$, or

f) $-(CH_2)_n-NH(2\text{-pyridyl})$;

R^3 is H, phenyl or C1-C4-alkyl;

R^4 is H or phenylsulfonyl;

R^5 and R^6 are hydrogen or when taken together from a six membered aromatic ring optionally substituted with one, two or three substituents selected from the group consisting of halo (F, Cl, Br, I), -CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, $-OR^8$, $-NO_2$, $-CF_3$, $-S(O)_rR^7$, $-NR^8R^9$, $-COR^8$, $-CO_2R^8$, $-CONR^8R^9$, phenyl, benzyl, phenylethyl;

R^7 is

a) phenyl,

b) C1-C4-alkyl,

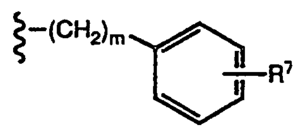
c) C1-C4-alkoxy, or

d) $-CF_3$;

R^8 and R^9 are independently

a) H,

b)



c) C3-C7-cycloalkyl,

d) C1-C8-alkyl;

R^{10} and R^{11} are independently

a) halo (F, Cl, Br, I),

b) -CN,

c) C1-C10-alkyl,

d) C3-C8-cycloalkyl,

e) C2-C10-alkenyl,

f) C2-C10-alkynyl,

g) $-OR^8$,

h) $-NO_2$,
i) $-CF_3$,
j) $-S(O)_rR^7$,
k) $-NR^8R^9$,
l) $-COR^9$,
m) $-CO_2R^8$
n) $-CONR^8R^9$;

R^{12} is
a) H,
b) C1-C4-alkyl,
c) phenyl,
d) benzyl
e) $-COR^7$
f) $-SO_2R^7$

m is 0 to 6;
n is 3 or 4;
p is 0 to 2;
r is 0 to 2;
t is 1 to 5
E is -CO-, $-SO_2-$, $-CH_2-$ or a single bond,
F is -CO-; and pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I) are those compounds wherein R^1 is phenyl and biphenyl containing 1-3 substituents selected from the series halo (F, Cl, Br, I), C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, $-R^8$, $-OR^8$, $-NO_2$, $-CF_3$, $-S(O)_rR^7$, $-NR^8R^9$, $-COR^8$, $-CO_2R^8$, $-CONR^8R^9$; NR^8COR^9;

R^2 is
a) $-(CH_2)_3-NHC(NH)NH_2$, or
b) $-(CH_2)_3-SC(NH)NH_2$.

More preferred are those preferred compounds wherein Z is $-(CH_2)_mCONR^8-$.

Most preferred are those more preferred compounds listed below:

N^1-(4-phenylbenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(3-phenoxybenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(1-fluorenonyl)-(*R*)-boroarginine, hydrochloride

N^1-(4-[1-butyl]benzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-benzoylbenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(5-phenyl-2-furoyl)-(*R*)-boroarginine, hydrochloride

N^1-(3-[*N*-benzyloxycarbonyl-*N*-methylamino]-4-[1-butyl]-benzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-phenyl-4-isoquinolyl)-(*R*)-boroarginine, hydrochloride

N^1-(4-cyclohexylbenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-phenylbenzoyl)-(R)-boroarginine, hydrochloride

Illustrative of the compounds of this invention are the following:

N^1-(4-phenylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(3-phenylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(3-phenoxybenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-[4-pyridyl]benzoyl)-(R)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-benzoylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(3-benzoylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-benzoylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(3-[*N*-benzyloxycarbonyl]aminobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(3-[*N*-benzyloxycarbonyl-*N*-methyl]aminobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-ethylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-*n*-propylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-isopropylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-*n*-butylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-*tert*-butylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-*n*-hexylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-cyclohexylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-[*N*-(2-phenylethyl)carbonyl]aminobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-*n*-butyloxybenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-[*N*-cyclopropylcarbonyl]aminobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-[*N*-cyclohexylcarbonyl]aminobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-[*N*-(4-methoxy)benzoyl]aminobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-[4-methoxy]phenylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-[2-phenyl]benzyloxycarbonylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-[1-naphthyl]benzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-[4-carboxy]phenylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(4-phenylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(3-phenylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(3-phenoxybenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-benzoylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(3-benzoylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-benzoylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(3-[*N*-benzyloxycarbonyl]aminobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(3-[*N*-benzyloxycarbonyl-*N*-methyl]aminobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-ethylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-*n*-propylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-isopropylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-*n*-butylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-*tert*-butylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-*n*-hexylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-cyclohexylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-[*N*-(2-phenylethyl)carbonyl]aminobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-*n*-butyloxybenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-[*N*-cyclopropylcarbonyl]aminobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-[*N*-cyclohexylcarbonyl]aminobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-[*N*-(4-methoxy)benzoyl]aminobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-[4-methoxy]phenylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-[2-phenylbenzyloxycarbonyl]benzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-[1-naphthyl]benzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(4-[4-carboxy]phenylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-([2-anthraquinonyl]carbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-([2-dioxothioxanthinonyl]carbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-([2-anthraquinonyl]carbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-([2-dioxothioxanthinonyl]carbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-([2-fluoren-9-onyl]carbonyl)-(*R*)-borothiohomoarginine (+)-pinanediol, hydrobromide

N^1-([2-fluoren-9-onyl]carbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-([2-fluoren-9-onyl]carbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-([3-fluoren-9-onyl]carbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-([3-fluoren-9-onyl]carbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-([4-fluoren-9-onyl]carbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-([4-fluoren-9-onyl]carbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(1-naphthoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(1-naphthoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-methyl-4-phenyl-5-methoxybenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-phenyl-5-fluorobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-phenyl-5-chlorobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-[4-carboxy]phenyl-5-trifluoromethylbenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide

N^1-(2-methyl-4-phenyl-5-methoxybenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-methyl-4-phenyl-5-fluorobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-methyl-4-phenyl-5-chlorobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-methyl-4-[4-carboxy]phenyl-5-trifluoromethylbenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-[5-phenyl]furylcarbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-[5-phenyl]thiophenylcarbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-[5-phenyl]furylcarbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide
N^1-(2-[5-phenyl]thiophen-ylcarbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide
N^1-(3-[6-phenyl]pyridylcarbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(3-[5-benzyloxy]pyridylcarbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(3-[6-phenyl]pyridylcarbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide
N^1-(3-[5-benzyloxy]pyridylcarbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide
N^1-(2-benzopyronylcarbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite

N^1-(2-benzopyronylcarbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide
N^1-(3-isoquinolinylcarbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-phenyl-4-isoquinolinylcarbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(3-isoquinolinylcarbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide
N^1-(2-phenyl-4-isoquinolinylcarbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide
N^1-(2-isoquinolinylcarbonyl)-(*R*)-boroarginine (+)-pinanediol, bisulfite
N^1-(2-isoquinolinylcarbonyl)-(*R*)-borothioarginine (+)-pinanediol, hydrobromide
N^1-(4-phenylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(3-phenylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(3-phenoxybenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(4-[4-pyridyl]benzoyl)-(R)-boroarginine, hydrochloride
N^1-(2-benzoylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(3-benzoylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(4-benzoylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(3-[*N*-benzyloxycarbonyl]aminobenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(3-[*N*-benzyloxycarbonyl-*N*-methyl]aminobenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(4-ethylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(4-*n*-propylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(4-isopropylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(4-*tert*-butylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(4-*n*-hexylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(4-cyclohexylbenzoyl)-(*R*)-boroarginine, hydrochloride
N^1-(2-[*N*-(2-phenylethyl)carbonyl]aminobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(4-*n*-butyloxybenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(4-[*N*-cyclopropylcarbonyl]aminobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(4-[*N*-cyclohexylcarbonyl]aminobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(4-[*N*-(4-methoxy)benzoyl]aminobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(4-[4-methoxy]phenylbenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-[2-phenyl]benzyloxycarbonylbenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-[1-naphthyl]benzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(4-[4-carboxy]phenylbenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-([2-anthraquinonyl]carbonyl)-(*R*)-boroarginine, hydrochloride

N^1-([2-dioxothioxanthinonyl]carbonyl)-(*R*)-boroarginine, hydrochloride

N^1-([2-fluoren-9-onyl]carbonyl)-(*R*)-boroarginine, hydrochloride

N^1-([3-fluoren-9-onyl]carbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(1-naphthoyl)-(*R*)-boroarginine, hydrochloride

N^1-([4-fluoren-9-onyl]carbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-methoxybenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-fluorobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-chlorobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-trifluoromethylbenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-[5-phenyl]furylcarbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-[5-phenyl]thiophenylcarbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-benzopyronylcarbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-isoquinolinylcarbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(3-isoquinolinylcarbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(2-phenyl-4-isoquinolinylcarbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(4-phenylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(3-phenylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(3-phenoxybenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-benzoylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(3-benzoylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-benzoylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(3-[*N*-benzyloxycarbonyl]aminobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(3-[*N*-benzyloxycarbonyl-*N*-methyl]aminobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-ethylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-*n*-propylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-isopropylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-*n*-butylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-*tert*-butylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-*n*-hexylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-cyclohexylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-[*N*-(2-phenylethyl)carbonyl]aminobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-*n*-butyloxybenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-[*N*-cyclopropylcarbonyl]aminobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-[*N*-cyclohexylcarbonyl]aminobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-[*N*-(4-methoxy)benzoyl]aminobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-[4-methoxy]phenylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-[2-phenylbenzyloxycarbonyl]benzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-[1-naphthyl]benzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-[4-carboxy]phenylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-([2-anthraquinonyl]carbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-([2-dioxothioxanthinonyl]carbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-([2-fluoren-9-onyl]carbonyl)-(*R*)-borothiohomoarginine, hydrochloride

N^1-([2-fluoren-9-onyl]carbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-([3-fluoren-9-onyl]carbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-([4-fluoren-9-onyl]carbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-(1-naphthoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-methoxybenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-fluorobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-chlorobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-trifluoromethylbenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-[5-phenyl]furylcarbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-[5-phenyl]thiophenylcarbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-(3-[6-phenyl]pyridylcarbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(3-[5-benzyloxy]pyridylcarbonyl)-(*R*)-boroarginine, hydrochloride

N^1-(3-[6-phenyl]pyridylcarbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-(3-[5-benzyloxy]pyridylcarbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-benzopyronylcarbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-(3-isoquinolinylcarbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-phenyl-4-isoquinolinylcarbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-(2-isoquinolinylcarbonyl)-(*R*)-borothioarginine, hydrochloride

N^1-(4-phenylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(3-phenylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(3-phenoxybenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-[4-pyridyl]benzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-benzoylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(3-benzoylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-benzoylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(3-[*N*-benzyloxycarbonyl]aminobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(3-[*N*-benzyloxycarbonyl-*N*-methyl]aminobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-ethylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-*n*-propylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-isopropylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-*tert*-butylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-*n*-hexylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-cyclohexylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-[*N*-(2-phenylethyl)carbonyl]aminobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-*n*-butyloxybenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-[*N*-cyclopropylcarbonyl]aminobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-[*N*-cyclohexylcarbonyl]aminobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-[*N*-(4-methoxy)benzoyl]aminobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-[4-methoxy]phenylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-[2-phenyl]benzyloxycarbonylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-[1-naphthyl]benzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-[4-carboxy]phenylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-([2-anthraquinonyl]carbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-([2-dioxothioxanthinonyl]carbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-([2-fluoren-9-onyl]carbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-([3-fluoren-9-onyl]carbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(1-naphthoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-([4-fluoren-9-onyl]carbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-phenyl-5-methoxybenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-phenyl-5-fluorobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-phenyl-5-chlorobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-trifluoromethylbenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-[5-phenyl]furylcarbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-[5-phenyl]thiophen-ylcarbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-benzopyronylcarbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-isoquinolinylcarbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(3-isoquinolinylcarbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(2-phenyl-4-isoquinolinylcarbonyl)-(*R*)-borolysine (+)-pinanediol, hydrochloride

N^1-(4-phenylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(3-phenylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(3-phenoxybenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(4-[4-pyridyl]benzoyl)-(R)-borolysine, hydrochloride

N^1-(2-benzoylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(3-benzoylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(4-benzoylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(3-[*N*-benzyloxycarbonyl]aminobenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(3-[*N*-benzyloxycarbonyl-*N*-methyl]aminobenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(4-ethylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(4-*n*-propylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(4-isopropylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(4-*tert*-butylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(4-*n*-hexylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(4-cyclohexylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-[*N*-(2-phenylethyl)carbonyl]aminobenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(4-*n*-butyloxybenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(4-[*N*-cyclopropylcarbonyl]aminobenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(4-[*N*-cyclohexylcarbonyl]aminobenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(4-[*N*-(4-methoxy)benzoyl]aminobenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(4-[4-methoxy]phenylbenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(2-[2-phenyl]benzyloxycarbonylbenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(2-[1-naphthyl]benzoyl)-(*R*)-borolysine, hydrochloride
N^1-(4-[4-carboxy]phenylbenzoyl)-(*R*)-borolysine, hydrochloride
N^1-([2-anthraquinonyl]carbonyl)-(*R*)-borolysine, hydrochloride
N^1-([2-dioxothioxanthinonyl]carbonyl)-(*R*)-borolysine, hydrochloride
N^1-([2-fluoren-9-onyl]carbonyl)-(*R*)-borolysine, hydrochloride
N^1-([3-fluoren-9-onyl]carbonyl)-(*R*)-borolysine, hydrochloride
N^1-(1-naphthoyl)-(*R*)-borolysine, hydrochloride
N^1-([4-fluoren-9-onyl]carbonyl)-(*R*)-borolysine, hydrochloride
N^1-(2-methyl-4-phenyl-5-methoxybenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(2-methyl-4-phenyl-5-fluorobenzoyl)-(*R*)-borolysine, hydrochloride
N^1-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-methyl-4-phenyl-5-chlorobenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-trifluoromethylbenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(*R*)-borolysine, hydrochloride

N^1-(2-[5-phenyl]furylcarbonyl)-(*R*)-borolysine, hydrochloride

N^1-(2-[5-phenyl]thiophen-ylcarbonyl)-(*R*)-borolysine, hydrochloride

N^1-(2-benzopyronylcarbonyl)-(*R*)-borolysine, hydrochloride

N^1-(2-isoquinolinylcarbonyl)-(*R*)-borolysine, hydrochloride

N^1-(3-isoquinolinylcarbonyl)-(*R*)-borolysine, hydrochloride

N^1-(2-phenyl-4-isoquinolinylcarbonyl)-(*R*)-borolysine, hydrochloride

N^1-(2-methyl-4-phenylbenzoyl)-R-borolysine, hydrochloride

N^1-(2-methyl-4-phenylbenzoyl)-R-borolysine, (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-phenylbenzoyl)-R-borothioarginine (+)-hydrobromide

N^1-(2-methyl-4-phenylbenzoyl)-R-borothioarginine (+)-pinanediol, hydrochloride

N^1-(2-methyl-4-phenylbenzoyl)-R-boroarginine (+)-hydrochloride

N^1-(2-methyl-4-phenylbenzoyl)-R-boroarginine (+)-pinanediol, bisulfite

Detailed Description of the Invention

Throughout the specification, the following conventional three-letter abbreviations for amino acid residues or amino acids apply:

Ala = alanine
Arg = arginine
Asn = asparagine
Asp = aspartic acid
Cys = cysteine
Gln = glutamine
Glu = glutamic acid
Gly = glycine
His = histidine
Ile = isoleucine
Leu = leucine
Lys = lysine
Met = methionine
Phe = phenylalanine
Pro = proline
Ser = serine
Thr = threonine
Trp = tryptophan
Tyr = tyrosine
Val = valine

The prefix "boro" indicates amino acid residues where the carboxy group is replaced by a boronic acid (Formula I, Y^1 and Y^2 = -OH).

The pinanediol boronic acid ester and the pinacol boronic acid ester are abbreviated "$-C_{10}H_{16}$" and

"$-C_6H_{12}$" respectively. Other illustrations of diols useful for deriving boronic acid esters are 1,2-ethanediol, 1,3-propanediol, 1,2-propanediol, 2,3-butanediol, 1,2-diisopropylethanediol, 5,6-decanediol, 1,2-dicyclohexylethanediol.

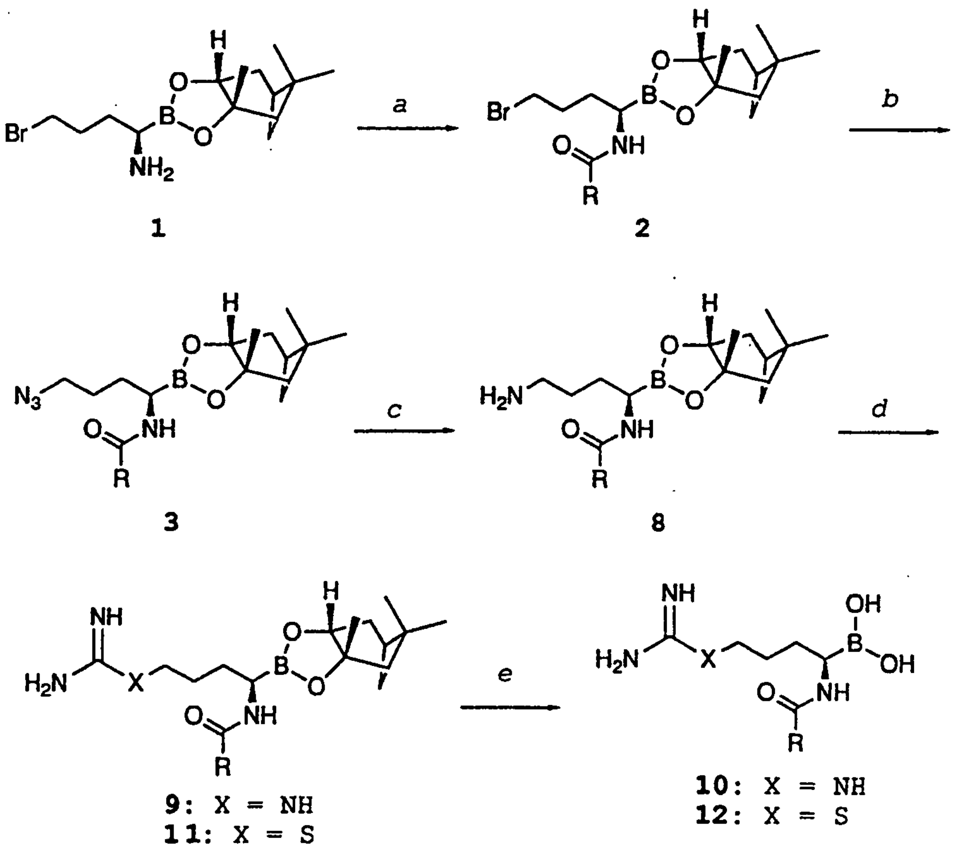
Note that throughout the text when an alkyl substituent is mentioned, the normal alkyl structure is meant (e.g. butyl is n-butyl) unless otherwise specified. However, in the definition of radicals above (e.g. R^3), both branched and straight chains are included in the scope of alkyl.

It is understood that many of the compounds of the present invention contain one or more chiral centers and that these stereoisomers may possess distinct physical and biological properties. The present invention comprises all of the stereoisomers or mixtures thereof. If the pure enantiomers or diastereomers are desired, they may be prepared using starting materials with the appropriate stereochemistry, or may be separated from mixtures of undesired stereoisomers by standard techniques, including chiral chromatography and recrystallization of diastereomeric salts.

Synthesis

The compounds of formula (I) can be prepared using the reactions and techniques described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being affected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the chemical transformations proposed and this will sometimes require judgment as to the order of synthetic steps or selection of particular process scheme used from that shown below in order to obtain a desired compound of the invention.

Scheme 1. Synthesis of Thrombin Inhibitors



Reagents: *a*. IBCF, NMM, RCO_2H, Et_3N, 0 °C, *b*. NaN_3, *c*. H_2, $Pd(OH)_2/C$, HCl, *d*. DMAP, aminoiminomethanesulfonic acid, *e*. phenylboronic acid

Amine hydrochloride **1** is readily available *via* the procedure of Kettner and Shenvi (EP 0293881 A2).

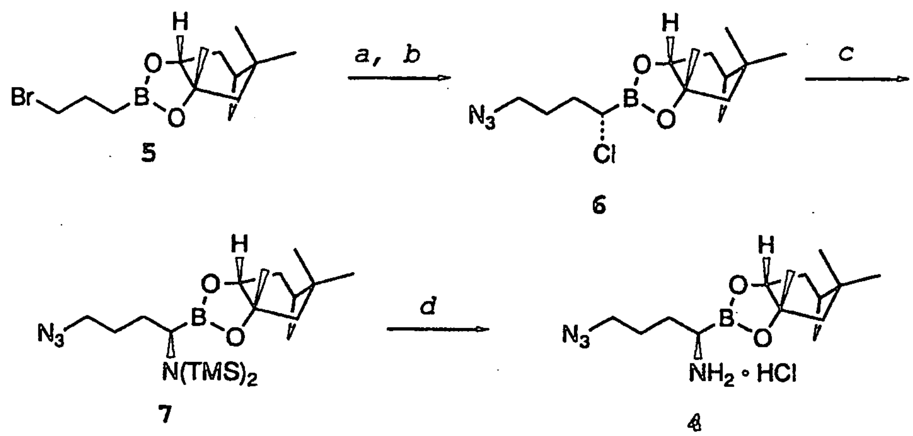
There are numerous synthetic methods by which to prepare amide **2**, however, competing with amide formation is the cyclization of **1** to afford a complex mixture containing the desired amide and the corresponding *N*-acylboroproline. Since purification at this stage is unfeasible, choosing the correct method for amide formation is crucial to obtaining **2** in a purity suitable for subsequent synthetic transformations.

Three methods are preferred for the preparation of **2**. In the first, a solution of **1** in tetrahydrofuran or dichloromethane at 0 °C is treated sequentially with the desired acid chloride followed by two equivalents of triethylamine. The mixture is then allowed to warm to room temperature overnight. The second method is the mixed anhydride procedure of Anderson, et. al. (*J. Am. Chem. Soc.* **1967**, *89*, 5012). In this method the isobutyl mixed anhydride is generated by dissolving the carboxylic acid component in tetrahydrofuran and adding one equivalent of *N*-methylmorpholine. The solution is cooled to 0 °C and one equivalent of isobutyl chloroformate is added. After 5 minutes, a solution of **1** in chloroform is added, followed by the addition of one equivalent of triethylamine. The mixture is typically stirred at 0 °C for one hour followed by one to several hours at room temperature. The third method for amide formation is the hydroxybenzotriazole/DCC method of König and Geiger (*Chem. Ber.* **1970**, *103*, 788-98). Thus, to a solution of **1** and the carboxylic acid component in dimethylformamide or tetrahydrofuran at 0 °C is added *N*-methylmorpholine, 1-hydroxybenzotriazole hydrate (2 eq) and DCC (1.05 eq). The solution is allowed to warm to room temperature overnight.

The preferred method for the preparation of azide **3** is by reaction of **2** with sodium azide (1.1 eq) in dimethylformamide at 70 °C for 2 hours.

The azide displacement may also be performed prior to amide formation. This is the preferred method in cases where the rate of amide formation is slow relative to the rate of cyclization. Azide 4 is prepared by a modification of the procedure of Kettner and Shenvi (EP 0293881 A2) as shown in Scheme 2. Thus, bromide **5** is reacted with sodium azide, followed by homologation to give **6**, chloride displacement to afford **7** and acidic hydrolysis to give 4. Amide formation between 4 and the carboxylic acid component then affords **3** directly.

Scheme 2. Synthesis of Azide 4



Reagents: *a.* NaN_3 *b.* $CHCl_2Li$, $ZnCl_2$, *c.* $LiN(TMS)_2$, *d.* 4M HCl, dioxane

Reduction of azide **3** to amine **8** may be accomplished by hydrogenation over precious metal catalysts. The preferred catalyst for this transformation is Pearlman's catalyst (palladium hydroxide on carbon). The amine is typically isolated as the hydrochloride salt. Isolation of **8** as the free base typically results in lowered yields. Salts of **8** which may confer superior physical properties may be preferred over the hydrochloride salt.

Formamidination of amine **8** may be accomplished using cyanamide. Due to the low reactivity of amine **8**,

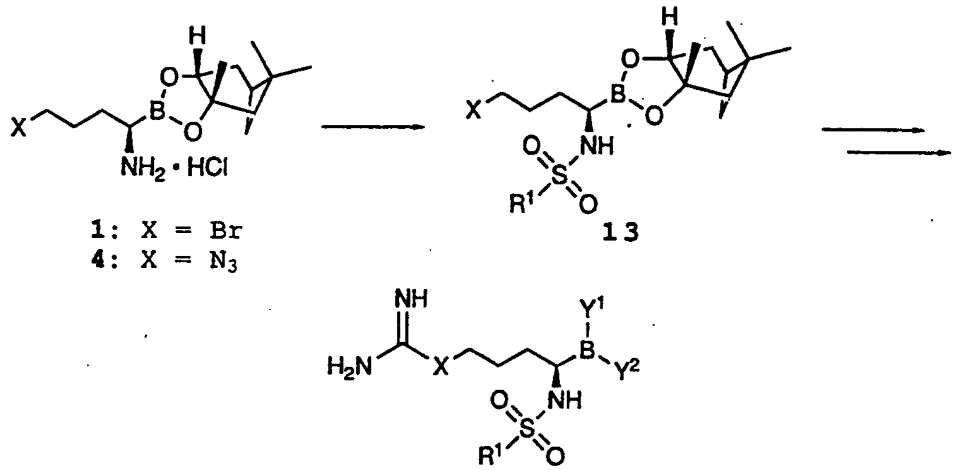
however, the preferred method for this transformation is reaction with 4-dimethylaminopyridine (DMAP) and aminoiminomethanesulfonic acid (AMSA, prepared by the method of Kim, et. al., *Tetrahedron Lett.* **1988**, *29*, 3183-6). This affords guanidine **9**, which is isolated as the bisulfite or hydrochloride salt.

Cleavage of pinanediol ester **9** may be accomplished using anhydrous boron trichloride according to the procedure of Matteson and Ray (*J. Am. Chem. Soc.* **1980**, *102*, 7588). This method, however, is strongly Lewis acidic and leads to partial destruction of the substrate. The preferred method for water soluble boronic acids is a transesterification reaction that is run in the presence of excess phenylboronic acid. The free boronic acid **10** may then be isolated using cation exchange chromatography.

The isothiouronium functionalized analogs **11/12** are prepared from bromide **2** according to the procedure of Kettner and Shenvi (EP 0293881 A2).

Inhibitors containing a sulfonamide in place of a carboxamide are prepared from either **1** or **4** by reaction with a sulfonyl chloride in the presence of a hindered amine (Scheme 3). The product sulfonamide **13** is then converted to the guanidinium **14** or isothiouronium **15** in the same manner as the corresponding carboxamides.

Scheme 3. Synthesis of Sulfonamides



1: X = Br
4: X = N_3

13

14: X = NH
15: X = S

Inhibitors containing the borolysine moiety are prepared analogously to those containing boroarginine according to Kettner and Shenvi (EP 0293881 A2).

Novel biaryls synthesized in this invention are prepared through palladium catalyzed coupling of an appropriate arylmetal species to the aryl halide of choice using the methods described in Negishi, et. al., *Org. Synth.* **1987**, *66*, 67-74, and references cited within.

EXAMPLE 1: N^1-(4-Phenylbenzoyl)boroarginine (+)-Pinanediol, Bisulfite

Part A: <u>(+)-Pinanediol 4-bromo-1(*R*)-(4-phenylbenzoyl)aminobutane-1-boronate</u>. To a solution of (+)-pinanediol 4-bromo-1(*R*)-aminobutane-1-boronate hydrochloride (5.00 g, 13.6 mmol) in dichloromethane (50 mL) at 0 °C was added 4-phenylbenzoyl chloride (4.97 g, 22.9 mmol) followed by *N*-methylmorpholine (4 mL, 36 mmol). After 1 hour, the cooling bath was removed and the mixture stirred at room temperature for 2 hours. The mixture was then diluted with ethyl acetate and washed with 0.1 *M* hydrochloric acid, saturated sodium bicarbonate and saturated sodium chloride. The organic phase was dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated *in vacuo* to afford 3.37 g (48%) of the desired amide, mass spectrum: $(M+H)^+$ = 510/512; ^1H NMR (300 MHz, $CDCl_3$) δ7.9 (2H, d, J = 8.3), 7.84 (1H, bs), 7.6 (2H, d, J = 8.3), 7.44 (5H, m), 4.37 (1H, m), 3.41 (1H, t, J = 6.9), 2.0 (10H, m) 1.49 (3H, s), 1.38 (1H, m), 1.29 (3H, s), 0.91 (3H, s).

Part B: <u>(+)-Pinanediol 4-azido-1(*R*)-(4-phenylbenzoyl)aminobutane-1-boronate</u>. To a solution of (+)-pinanediol 4-bromo-1(*R*)-(4-phenylbenzoyl)aminobutane-1-boronate (3.37 g, 6.60 mmol) in dimethylformamide (6 mL) was added sodium azide (547 mg, 8.41 mmol). The resulting mixture was heated at 70 °C for 2 hours, cooled to room temperature, and diluted with ethyl acetate. The mixture was then washed with water, saturated sodium chloride and dried over anhydrous magnesium sulfate. Filtration, followed by concentration of the filtrate *in vacuo* gave 3.04 g (97%) of the desired azide, mass spectrum: $(M+H)^+$ = 473; ^1H NMR (300 MHz, $CDCl_3$) δ7.89 (2H, d, J = 8.3), 7.75 (1H, bs), 7.3 (7H, m), 4.32 (1H, m), 3.32 (1H, m), 2.0 (10H, m) 1.48 (3H, s), 1.3 (4H, m), 0.9 (3H, s).

Part C: <u>*N*[1]-(4-Phenylbenzoyl)boroornithine (+)-pinanediol, hydrochloride</u>. To a solution of (+)-pinanediol 4-azido-1(*R*)-(4-phenylbenzoyl)aminobutane-1-boronate (3.04 g, 6.44 mmol) in methanol (30 mL) was added Pearlman's catalyst $Pd(OH)_2/C$, 200 mg) and 1 *M* hydrochloric acid (6.5 mL, 6.5 mmol). The mixture was placed on a Parr apparatus and hydrogenated at 50 psi for 3 hours. The mixture was filtered using Celite™, washed with methanol and the filtrate concentrated *in vacuo*. The resulting amorphous solid was dissolved in water and washed with ether. The aqueous phase was then concentrated *in vacuo* and crystallized from ethyl acetate-hexanes, giving 1.52 g (49%) of the desired amine hydrochloride, mass spectrum: $(M+H)^+ = 447$; mp: 157-170 °C; ^1H NMR (400 MHz, $CDCl_3/DMSO-d_6$) δ9.88 (1H, bs), 8.18, (2H, d, J = 8.3), 8.13 (3H, bs), 7.68 (2H, d, J = 8.3), 7.61 (2H, d J = 7.0), 7.45 (2H, d, J = 7.0), 7.37 (1H, d, J = 7.30), 4.20 (1H, d, J = 6.3), 2.99 (1H, m), 2.87 (2H, m), 2.31 (1H, m), 2.13 (1H, m), 1.84 (7H, m), 1.56 (1H, d, J = 10.0), 1.42 (3H, s), 1.29 (3H, s), 0.89 (3H, s).

Part D: <u>*N*[1]-(4-Phenylbenzoyl)boroarginine (+)-pinanediol, bisulfite</u>. To a solution of *N*[1]-(4-phenylbenzoyl)boroornithine (+)-pinanediol, hydrochloride (80 mg, 0.17 mmol) in ethanol (2 mL) was added 4-dimethylaminopyridine (40 mg, 0.33 mmol). After 15 minutes, aminoiminomethanesulfonic acid (40 mg, 0.32 mmol) was added and the resulting mixture heated at reflux for 3 hours. After cooling to room temperature, the mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in chloroform and washed with 0.1 *M* hydrochloric acid, water and dried over anhydrous magnesium sulfate. Filtration, followed by concentration of the filtrate *in vacuo* afforded 73 mg

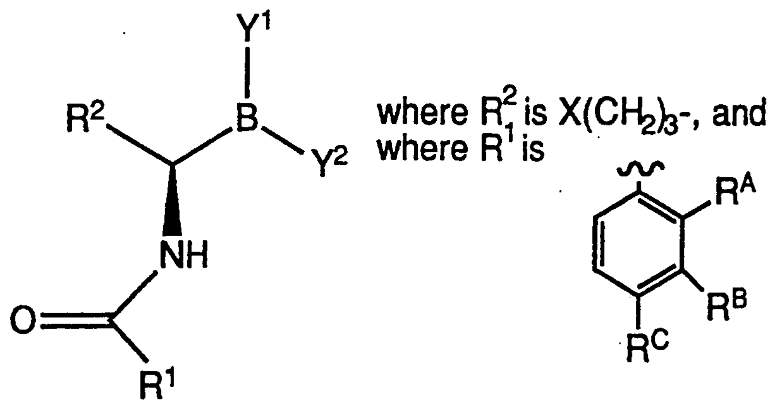
(84%) of the desired guanidine, mass spectrum: $(M+H)^+$ = 489; ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ9.48 (1H, bs), 8.10 (2H, d, J = 8.1), 8.07 (1H, bs), 7.75 (1H, bs), 7.54 (2H, d, J = 8.3), 7.48 (2H, d, J = 7.0), 7.35 (3H, m), 7.06 (4H, bs), 4.19 (1H, bd, J = 8.3), 3.1 (2H, m), 2.84 (1H, m), 2.29 (1H, m), 2.12 (1H, m), 1.96 (1H, m), 1.75 (6H, m), 1.47 (1H, d, J = 10.2), 1.40 (3H, s), 1.24 (3H, s), 0.83 (3H, s).

EXAMPLE 34: (+)-Pinanediol 4-(Formamidino)thio-1(*R*)-(4-phenylbenzoyl)aminobutane-1-boronate, Hydrobromide

<u>(+)-Pinanediol 4-(formamidino)thio-1(*R*)-(4-phenylbenzoyl)aminobutane-1-boronate, hydrobromide</u>. To a solution of (+)-pinanediol 4-bromo-1(*R*)-(4-phenylbenzoyl)aminobutane-1-boronate (200 mg, 0.392 mmol) in methanol (3 mL) was added thiourea (120 mg, 1.58 mmol). The reaction was stirred at room temperature for 3 days. The mixture was concentrated *in vacuo,* the residue dissolved in water and washed with ether. Concentration of the aqueous portion afforded 80 mg (35%) of the desired isothiourea, mass spectrum: $(M+H)^+$ = 506; ^1H NMR (300 MHz, $CDCl_3$) δ8.15 (2H, d, J = 8.4), 7.61 (2H, d, J = 8.4), 7.52 (2H, m), 7.38 (3H, m), 6.47 (1H, bs), 4.23 (1H, dd, J = 6.6, 1.9), 3.24 (1H, m), 3.14, (1H, m), 2.96, (1H, m), 2.32 (1H, m), 2.15 (1H, m), 1.99 (1H, m), 1.78 (6H, m), 1.48 (1H, d, J = 10.1), 1.42 (3H, s), 1.27 (3H, s), 0.86 (3H, s).

The compounds listed in Tables 1-12 can be prepared using the above examples.

TABLE 1



Ex	X	R^A	R^B	R^C	Y^1, Y^2	Phys Data
1	$NHC(NH)NH_2$	H	H	Ph	(+)-pinanediol	A
2	$NHC(NH)NH_2$	H	Ph	H	(+)-pinanediol	
3	$NHC(NH)NH_2$	H	OPh	Ph	(+)-pinanediol	B
4	$NHC(NH)NH_2$	H	H	4-pyridyl	(+)-pinanediol	C
5	$NHC(NH)NH_2$	COPh	H	H	(+)-pinanediol	
6	$NHC(NH)NH_2$	H	COPh	H	(+)-pinanediol	
7	$NHC(NH)NH_2$	H	H	COPh	(+)-pinanediol	
8	$NHC(NH)NH_2$	H	NHCbz	H	(+)-pinanediol	
9	$NHC(NH)NH_2$	H	NMeCbz	H	(+)-pinanediol	
10	$NHC(NH)NH_2$	H	H	Et	(+)-pinanediol	
11	$NHC(NH)NH_2$	H	H	n-Pr	(+)-pinanediol	
12	$NHC(NH)NH_2$	H	H	i-Pr	(+)-pinanediol	
13	$NHC(NH)NH_2$	H	H	n-Bu	(+)-pinanediol	
14	$NHC(NH)NH_2$	H	H	t-Bu	(+)-pinanediol	
15	$NHC(NH)NH_2$	H	H	n-hexyl	(+)-pinanediol	
16	$NHC(NH)NH_2$	H	H	cyclohexyl	(+)-pinanediol	
17	$NHC(NH)NH_2$	$NHCO(CH_2)_2Ph$	H	H	(+)-pinanediol	

18	NHC(NH)NH_2	H	H	O-n-Bu	(+)-pinanediol	
19	NHC(NH)NH_2	H	H	NHCOcyclopropyl	(+)-pinanediol	

Ex	X	R^A	R^B	R^C	Y^1,Y^2	Phys Data
20	NHC(NH)NH_2	H	H	NHCO-cyclohexyl	(+)-pinanediol	
21	NHC(NH)NH_2	H	H	NHCO(4-C_6H_4OMe)	(+)-pinanediol	
22	NHC(NH)NH_2	H	H	4-C_6H_4OMe	(+)-pinanediol	
23	NHC(NH)NH_2	CO_2CH_2(2-C_6H_4Ph)	H	H	(+)-pinanediol	
24	NHC(NH)NH_2	H	H	1-naphthyl	(+)-pinanediol	
25	NHC(NH)NH_2	H	H	4-$C_6H_4CO_2H$	(+)-pinanediol	
26	NHC(NH)NH_2	COPh	H	Me	(+)-pinanediol	
27	NHC(NH)NH_2	H	NHCbz	n-Bu	(+)-pinanediol	
28	NHC(NH)NH_2	H	NMeCbz	n-Bu	(+)-pinanediol	
29	NHC(NH)NH_2	Me	H	Ph	(+)-pinanediol	QQ
30	NHC(NH)NH_2	Me	H	4-$C_6H_4CO_2H$	(+)-pinanediol	
31	NHC(NH)NH_2	H	H	4-$C_6H_4CO_2Me$	(+)-pinanediol	
32	NHC(NH)NH_2	Me	H	4-$C_6H_4CO_2Me$	(+)-pinanediol	
33	NHC(NH)NH_2	H	OMe	Ph	(+)-pinanediol	
34	SC(NH)NH_2	H	H	Ph	(+)-pinanediol	D
35	SC(NH)NH_2	H	Ph	H	(+)-pinanediol	E
36	SC(NH)NH_2	H	OPh	H	(+)-pinanediol	F
37	SC(NH)NH_2	COPh	H	H	(+)-pinanediol	G
38	SC(NH)NH_2	H	COPh	H	(+)-pinanediol	H
39	SC(NH)NH_2	H	H	COPh	(+)-pinanediol	I
40	SC(NH)NH_2	H	NHCbz	H	(+)-pinanediol	J
41	SC(NH)NH_2	H	NMeCbz	H	(+)-pinanediol	K
42	SC(NH)NH_2	H	H	Et	(+)-pinanediol	L
43	SC(NH)NH_2	H	H	n-Pr	(+)-pinanediol	M
44	SC(NH)NH_2	H	H	i-Pr	(+)-pinanediol	N
45	SC(NH)NH_2	H	H	n-Bu	(+)-pinanediol	O
46	SC(NH)NH_2	H	H	t-Bu	(+)-pinanediol	P
47	SC(NH)NH_2	H	H	n-hexyl	(+)-pinanediol	Q
48	SC(NH)NH_2	H	H	cyclohexyl	(+)-pinanediol	R
49	SC(NH)NH_2	$NHCOCH_2CH_2Ph$	H	H	(+)-pinanediol	S
50	SC(NH)NH_2	H	H	O-n-Bu	(+)-pinanediol	T

51	$SC(NH)NH_2$	H	H	NHCOcyclopropyl	(+)-pinanediol	U

Ex	X	R^A	R^B	R^C	Y^1, Y^2	Phys Data
52	$SC(NH)NH_2$	H	H	NHCOcyclohexyl	(+)-pinanediol	V
53	$SC(NH)NH_2$	H	H	$NHCO(4\text{-}C_6H_4OMe)$	(+)-pinanediol	W
54	$SC(NH)NH_2$	H	H	$4\text{-}C_6H_4OMe$	(+)-pinanediol	X
55	$SC(NH)NH_2$	$CO_2CH_2(2\text{-}C_6H_4Ph)$	H	H	(+)-pinanediol	Y
56	$SC(NH)NH_2$	H	H	1-naphthyl	(+)-pinanediol	
57	$SC(NH)NH_2$	H	H	$4\text{-}C_6H_4CO_2H$	(+)-pinanediol	
58	$SC(NH)NH_2$	H	NHCbz	n-Bu	(+)-pinanediol	Z
59	$SC(NH)NH_2$	H	NMeCbz	n-Bu	(+)-pinanediol	AA
60	$SC(NH)NH_2$	COPh	H	Me	(+)-pinanediol	BB
61	$SC(NH)NH_2$	H	H	4-pyridyl	(+)-pinanediol	
62	$SC(NH)NH_2$	Me	H	$4\text{-}C_6H_4CO_2H$	(+)-pinanediol	
63	$SC(NH)NH_2$	H	H	$4\text{-}C_6H_4CO_2Me$	(+)-pinanediol	
64	$SC(NH)NH_2$	Me	H	$4\text{-}C_6H_4CO_2Me$	(+)-pinanediol	
65	$SC(NH)NH_2$	Me	H	Ph	(+)-pinanediol	
66	$SC(NH)NH_2$	H	OMe	Ph	(+)-pinanediol	
67	CH_2NH_2	H	H	Ph	(+)-pinanediol	
68	CH_2NH_2	H	Ph	H	(+)-pinanediol	
69	CH_2NH_2	H	OPh	H	(+)-pinanediol	
70	CH_2NH_2	COPh	H	H	(+)-pinanediol	
71	CH_2NH_2	H	COPh	H	(+)-pinanediol	
72	CH_2NH_2	H	H	COPh	(+)-pinanediol	
73	CH_2NH_2	H	NHCbz	H	(+)-pinanediol	
74	CH_2NH_2	H	NMeCbz	H	(+)-pinanediol	
75	CH_2NH_2	H	H	Et	(+)-pinanediol	
76	CH_2NH_2	H	H	n-Pr	(+)-pinanediol	
77	CH_2NH_2	H	H	i-Pr	(+)-pinanediol	
78	CH_2NH_2	H	H	n-Bu	(+)-pinanediol	
79	CH_2NH_2	H	H	t-Bu	(+)-pinanediol	
80	CH_2NH_2	H	H	n-hexyl	(+)-pinanediol	
81	CH_2NH_2	H	H	cyclohexyl	(+)-pinanediol	
82	CH_2NH_2	$NHCOCH_2CH_2Ph$	H	H	(+)-pinanediol	
83	CH_2NH_2	H	H	O-n-Bu	(+)-pinanediol	

84	CH_2NH_2	H	H	NHCOcyclopropyl	(+)-pinanediol	
Ex	**X**	**R^A**	**R^B**	**R^C**	**Y^1, Y^2**	**Phys Data**
85	CH_2NH_2	H	H	NHCOcyclohexyl	(+)-pinanediol	
86	CH_2NH_2	H	H	NHCO(4-C_6H_4OMe)	(+)-pinanediol	
87	CH_2NH_2	H	H	4-C_6H_4OMe	(+)-pinanediol	
88	CH_2NH_2	CO_2CH_2(2-C_6H_4Ph)	H	H	(+)-pinanediol	
89	CH_2NH_2	H	H	1-naphthyl	(+)-pinanediol	
90	CH_2NH_2	H	H	4-$C_6H_4CO_2H$	(+)-pinanediol	
91	CH_2NH_2	H	NHCbz	n-Bu	(+)-pinanediol	
92	CH_2NH_2	H	NMeCbz	n-Bu	(+)-pinanediol	
93	CH_2NH_2	COPh	H	Me	(+)-pinanediol	
94	CH_2NH_2	H	H	4-pyridyl	(+)-pinanediol	
95	CH_2NH_2	Me	H	4-$C_6H_4CO_2H$	(+)-pinanediol	
96	CH_2NH_2	H	H	4-$C_6H_4CO_2Me$	(+)-pinanediol	
97	CH_2NH_2	Me	H	4-$C_6H_4CO_2Me$	(+)-pinanediol	
98	CH_2NH_2	Me	H	Ph	(+)-pinanediol	
99	CH_2NH_2	H	OMe	Ph	(+)-pinanediol	
100	CH_2NH_2	H	OMe	Ph	H,H	
101	NHC(NH)NH_2	H	H	Ph	H,H	
102	NHC(NH)NH_2	H	Ph	H	H,H	
103	NHC(NH)NH_2	H	OPh	Ph	H,H	
104	NHC(NH)NH_2	H	H	4-pyridyl	H,H	
105	NHC(NH)NH_2	COPh	H	H	H,H	
106	NHC(NH)NH_2	H	COPh	H	H,H	
107	NHC(NH)NH_2	H	H	COPh	H,H	
108	NHC(NH)NH_2	H	NHCbz	H	H,H	
109	NHC(NH)NH_2	H	NMeCbz	H	H,H	
110	NHC(NH)NH_2	H	H	Et	H,H	
111	NHC(NH)NH_2	H	H	n-Pr	H,H	
112	NHC(NH)NH_2	H	H	i-Pr	H,H	
113	NHC(NH)NH_2	H	H	n-Bu	H,H	
114	NHC(NH)NH_2	H	H	t-Bu	H,H	
115	NHC(NH)NH_2	H	H	n-hexyl	H,H	
116	NHC(NH)NH_2	H	H	cyclohexyl	H,H	
117	NHC(NH)NH_2	NHCO$(CH_2)_2$Ph	H	H	H,H	

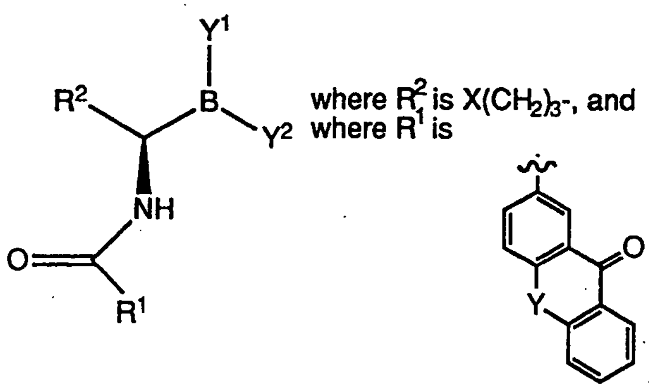
Ex	X	R^A	R^B	R^C	Y^1,Y^2	Phys Data
118	NHC(NH)NH_2	H	H	O-n-Bu	H,H	
119	NHC(NH)NH_2	H	H	NHCOcyclopropyl	H,H	
120	NHC(NH)NH_2	H	H	NHCO-cyclohexyl	H,H	
121	NHC(NH)NH_2	H	H	NHCO(4-C_6H_4OMe)	H,H	
122	NHC(NH)NH_2	H	H	4-C_6H_4OMe	H,H	
123	NHC(NH)NH_2	CO_2CH_2(2-C_6H_4Ph)	H	H	H,H	
124	NHC(NH)NH_2	H	H	1-naphthyl	H,H	
125	NHC(NH)NH_2	H	H	4-$C_6H_4CO_2H$	H,H	
126	NHC(NH)NH_2	COPh	H	Me	H,H	
127	NHC(NH)NH_2	H	NHCbz	n-Bu	H,H	
128	NHC(NH)NH_2	H	NMeCbz	n-Bu	H,H	
129	NHC(NH)NH_2	Me	H	Ph	H,H	
130	NHC(NH)NH_2	Me	H	4-$C_6H_4CO_2H$	H,H	
131	NHC(NH)NH_2	H	H	4-$C_6H_4CO_2Me$	H,H	
132	NHC(NH)NH_2	Me	H	4-$C_6H_4CO_2Me$	H,H	
133	NHC(NH)NH_2	H	OMe	Ph	H,H	
134	SC(NH)NH_2	H	H	Ph	H,H	
135	SC(NH)NH_2	H	Ph	H	H,H	
136	SC(NH)NH_2	H	OPh	H	H,H	
137	SC(NH)NH_2	COPh	H	H	H,H	
138	SC(NH)NH_2	H	COPh	H	H,H	
139	SC(NH)NH_2	H	H	COPh	H,H	
140	SC(NH)NH_2	H	NHCbz	H	H,H	
141	SC(NH)NH_2	H	NMeCbz	H	H,H	
142	SC(NH)NH_2	H	H	Et	H,H	
143	SC(NH)NH_2	H	H	n-Pr	H,H	
144	SC(NH)NH_2	H	H	i-Pr	H,H	
145	SC(NH)NH_2	H	H	n-Bu	H,H	
146	SC(NH)NH_2	H	H	t-Bu	H,H	
147	SC(NH)NH_2	H	H	n-hexyl	H,H	
148	SC(NH)NH_2	H	H	cyclohexyl	H,H	
149	SC(NH)NH_2	$NHCOCH_2CH_2Ph$	H	H	H,H	
150	SC(NH)NH_2	H	H	O-n-Bu	H,H	

Ex X R^A R^B R^C Y^1,Y^2 Phys

						Data
151	SC(NH)NH2	H	H	NHCO(CH2)2phenyl	H,H	RR
152	SC(NH)NH2	H	H	NHCOcyclohexyl	H,H	
153	SC(NH)NH2	H	H	NHCO(4-C6H4OMe)	H,H	
154	SC(NH)NH2	H	H	4-C6H4OMe	H,H	
155	SC(NH)NH2	CO2CH2(2-C6H4Ph)	H	H	H,H	
156	SC(NH)NH2	H	H	1-naphthyl	H,H	
157	SC(NH)NH2	H	H	4-C6H4CO2H	H,H	
158	SC(NH)NH2	H	NHCbz	n-Bu	H,H	
159	SC(NH)NH2	H	NMeCbz	n-Bu	H,H	
160	SC(NH)NH2	COPh	H	Me	H,H	
161	SC(NH)NH2	H	H	4-pyridyl	H,H	
162	SC(NH)NH2	Me	H	4-C6H4CO2H	H,H	
163	SC(NH)NH2	H	H	4-C6H4CO2Me	H,H	
164	SC(NH)NH2	Me	H	4-C6H4CO2Me	H,H	
165	SC(NH)NH2	Me	H	Ph	H,H	
166	SC(NH)NH2	H	OMe	Ph	H,H	
167	CH2NH2	H	H	Ph	H,H	
168	CH2NH2	H	Ph	H	H,H	
169	CH2NH2	H	OPh	H	H,H	
170	CH2NH2	COPh	H	H	H,H	
171	CH2NH2	H	COPh	H	H,H	
172	CH2NH2	H	H	COPh	H,H	
173	CH2NH2	H	NHCbz	H	H,H	
174	CH2NH2	H	NMeCbz	H	H,H	
175	CH2NH2	H	H	Et	H,H	
176	CH2NH2	H	H	n-Pr	H,H	
177	CH2NH2	H	H	i-Pr	H,H	
178	CH2NH2	H	H	n-Bu	H,H	
179	CH2NH2	H	H	t-Bu	H,H	
180	CH2NH2	H	H	n-hexyl	H,H	
181	CH2NH2	H	H	cyclohexyl	H,H	
182	CH2NH2	NHCOCH2CH2Ph	H	H	H,H	
183	CH2NH2	H	H	O-n-Bu	H,H	
Ex	X	R^A	R^B	R^C	Y^1,Y^2	Phys Data

184	CH_2NH_2	H	H	NHCOcyclopropyl	H,H
185	CH_2NH_2	H	H	NHCOcyclohexyl	H,H
186	CH_2NH_2	H	H	NHCO(4-C_6H_4OMe)	H,H
187	CH_2NH_2	H	H	4-C_6H_4OMe	H,H
188	CH_2NH_2	CO_2CH_2(2-C_6H_4Ph)	H	H	H,H
189	CH_2NH_2	H	H	1-naphthyl	H,H
190	CH_2NH_2	H	H	4-$C_6H_4CO_2H$	H,H
191	CH_2NH_2	H	NHCbz	n-Bu	H,H
192	CH_2NH_2	H	NMeCbz	n-Bu	H,H
193	CH_2NH_2	COPh	H	Me	H,H
194	CH_2NH_2	H	H	4-pyridyl	H,H
195	CH_2NH_2	Me	H	4-$C_6H_4CO_2H$	H,H
196	CH_2NH_2	H	H	4-$C_6H_4CO_2$Me	H,H
197	CH_2NH_2	Me	H	4-$C_6H_4CO_2$Me	H,H
198	CH_2NH_2	Me	H	Ph	H,H

TABLE 2

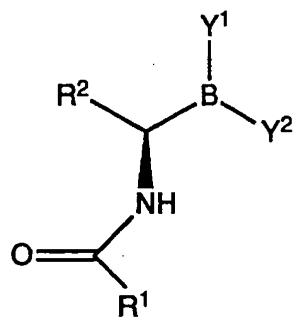


Ex	X	Y	Y^1,Y^2	Phys Data
199	CH_2NH_2	CO	(+)-pinanediol	
200	CH_2NH_2	SO_2	(+)-pinanediol	
201	NHC(NH)NH_2	CO	(+)-pinanediol	

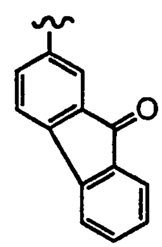
Ex	X	Y	Y^1,Y^2	Phys

				Data
202	NHC(NH)NH_2	SO_2	(+)-pinanediol	
203	SC(NH)NH_2	CO	(+)-pinanediol	CC
204	SC(NH)NH_2	SO_2	(+)-pinanediol	DD
205	CH_2NH_2	CO	H,H	
206	CH_2NH_2	SO_2	H,H	
207	NHC(NH)NH_2	CO	H,H	
208	NHC(NH)NH_2	SO_2	H,H	
209	SC(NH)NH_2	CO	H,H	
210	SC(NH)NH_2	SO_2	H,H	

TABLE 3



where R^2 is $XCH_2(CH_2)_tCH_2$-, and where R^1 is

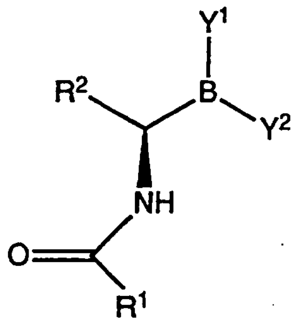


Ex	X	t	Y^1,Y^2	Phys Data
211	NH_2	2	(+)-pinanediol	
212	SC(NH)NH_2	2	(+)-pinanediol	EE
213	SC(NH)NH_2	1	(+)-pinanediol	FF
214	NHC(NH)NH_2	2	(+)-pinanediol	
215	NHC(NH)NH_2	1	(+)-pinanediol	
216	NH_2	2	H,H	
217	SC(NH)NH_2	2	H,H	

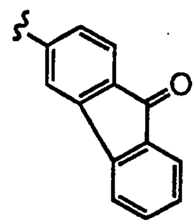
Ex	X	T	Y^1,Y^2	Phys

				Data
218	SC(NH)NH2	1	H,H	
219	NHC(NH)NH2	2	H,H	
220	NHC(NH)NH2	1	H,H	

TABLE 4

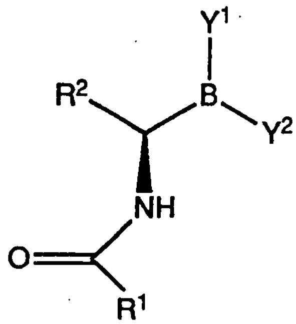


where R^2 is $X(CH_2)_3$-, and where R^1 is

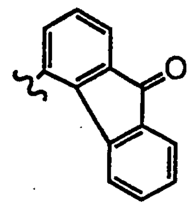


Ex	X	Y^1, Y^2	Phys Data
221	CH_2NH_2	(+)-pinanediol	
222	NHC(NH)NH2	(+)-pinanediol	
223	SC(NH)NH2	(+)-pinanediol	GG
224	CH_2NH_2	H,H	
225	NHC(NH)NH2	H,H	
226	SC(NH)NH2	H,H	

TABLE 5

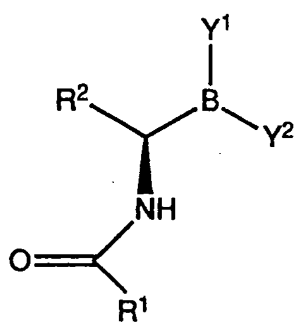


where R^2 is $X(CH_2)_3$-, and where R^1 is

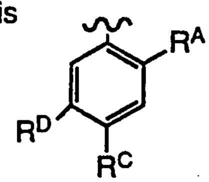


Ex	X	Y^1, Y^2	Phys Data
227	CH_2NH_2	(+)-pinanediol	
228	$NHC(NH)NH_2$	(+)-pinanediol	
229	$SC(NH)NH_2$	(+)-pinanediol	HH
230	CH_2NH_2	H,H	
231	$NHC(NH)NH_2$	H,H	
232	$SC(NH)NH_2$	H,H	

TABLE 6



where R^2 is $X(CH_2)_3$-, and where R^1 is



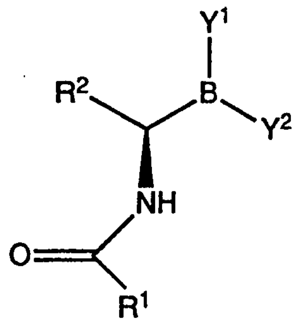
Ex	X	R^A	R^C	R^D	Y^1, Y^2	Phys Data
233	NHC(NH)NH_2	Me	Ph	OMe	(+)-pinanediol	
234	NHC(NH)NH_2	Me	Ph	$CONH_2$	(+)-pinanediol	
235	NHC(NH)NH_2	Me	Ph	F	(+)-pinanediol	
236	NHC(NH)NH_2	Me	Ph	CF_3	(+)-pinanediol	
237	NHC(NH)NH_2	Me	Ph	Cl	(+)-pinanediol	
238	NHC(NH)NH_2	Me	Ph	OH	(+)-pinanediol	
239	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	OMe	(+)-pinanediol	
240	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	CONH2	(+)-pinanediol	
241	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	F	(+)-pinanediol	
242	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	CF_3	(+)-pinanediol	
243	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	Cl	(+)-pinanediol	
244	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	OH	(+)-pinanediol	
245	SC(NH)NH_2	Me	Ph	OMe	(+)-pinanediol	
246	SC(NH)NH_2	Me	Ph	$CONH_2$	(+)-pinanediol	
247	SC(NH)NH_2	Me	Ph	F	(+)-pinanediol	
248	SC(NH)NH_2	Me	Ph	CF_3	(+)-pinanediol	
249	SC(NH)NH_2	Me	Ph	Cl	(+)-pinanediol	
250	SC(NH)NH_2	Me	Ph	OH	(+)-pinanediol	
251	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	OMe	(+)-pinanediol	
252	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	$CONH_2$	(+)-pinanediol	
253	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	F	(+)-pinanediol	
254	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	CF_3	(+)-pinanediol	
255	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	Cl	(+)-pinanediol	
256	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	OH	(+)-pinanediol	
257	CH_2NH_2	Me	Ph	OMe	(+)-pinanediol	
258	CH_2NH_2	Me	Ph	$CONH_2$	(+)-pinanediol	
259	CH_2NH_2	Me	Ph	F	(+)-pinanediol	
260	CH_2NH_2	Me	Ph	CF_3	(+)-pinanediol	
261	CH_2NH_2	Me	Ph	Cl	(+)-pinanediol	
262	CH_2NH_2	Me	Ph	OH	(+)-pinanediol	
263	CH_2NH_2	Me	4-$C_6H_4CO_2H$	OMe	(+)-pinanediol	
264	CH_2NH_2	Me	4-$C_6H_4CO_2H$	CONH2	(+)-pinanediol	
265	CH_2NH_2	Me	4-$C_6H_4CO_2H$	F	(+)-pinanediol	
266	CH_2NH_2	Me	4-$C_6H_4CO_2H$	CF_3	(+)-pinanediol	

| Ex | X | R^A | R^C | R^D | Y^1, Y^2 | Phys Data |

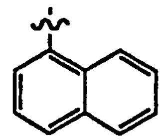
267	CH_2NH_2	Me	4-$C_6H_4CO_2H$	Cl	(+)-pinanediol	
268	CH_2NH_2	Me	4-$C_6H_4CO_2H$	OH	(+)-pinanediol	
269	NHC(NH)NH_2	Me	Ph	OMe	H,H	
270	NHC(NH)NH_2	Me	Ph	$CONH_2$	H,H	
271	NHC(NH)NH_2	Me	Ph	F	H,H	
272	NHC(NH)NH_2	Me	Ph	CF_3	H,H	
273	NHC(NH)NH_2	Me	Ph	Cl	H,H	
274	NHC(NH)NH_2	Me	Ph	OH	H,H	
275	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	OMe	H,H	
276	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	CONH2	H,H	
277	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	F	H,H	
278	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	CF_3	H,H	
279	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	Cl	H,H	
280	NHC(NH)NH_2	Me	4-$C_6H_4CO_2H$	OH	H,H	
281	SC(NH)NH_2	Me	Ph	OMe	H,H	
282	SC(NH)NH_2	Me	Ph	$CONH_2$	H,H	
283	SC(NH)NH_2	Me	Ph	F	H,H	
284	SC(NH)NH_2	Me	Ph	CF_3	H,H	
285	SC(NH)NH_2	Me	Ph	Cl	H,H	
286	SC(NH)NH_2	Me	Ph	OH	H,H	
287	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	OMe	H,H	
288	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	$CONH_2$	H,H	
289	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	F	H,H	
290	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	CF_3	H,H	
291	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	Cl	H,H	
292	SC(NH)NH_2	Me	4-$C_6H_4CO_2H$	OH	H,H	
293	CH_2NH_2	Me	Ph	OMe	H,H	
294	CH_2NH_2	Me	Ph	$CONH_2$	H,H	
295	CH_2NH_2	Me	Ph	F	H,H	
296	CH_2NH_2	Me	Ph	CF_3	H,H	
297	CH_2NH_2	Me	Ph	Cl	H,H	
298	CH_2NH_2	Me	Ph	OH	H,H	
299	CH_2NH_2	Me	4-$C_6H_4CO_2H$	OMe	H,H	
300	CH_2NH_2	Me	4-$C_6H_4CO_2H$	CONH2	H,H	
Ex	X	R^A	R^C	R^D	Y^1,Y^2	Phys Data
301	CH_2NH_2	Me	4-$C_6H_4CO_2H$	F	H,H	

302	CH_2NH_2	Me	$4\text{-}C_6H_4CO_2H$	CF_3	H,H
303	CH_2NH_2	Me	$4\text{-}C_6H_4CO_2H$	Cl	H,H
304	CH_2NH_2	Me	$4\text{-}C_6H_4CO_2H$	OH	H,H

TABLE 7

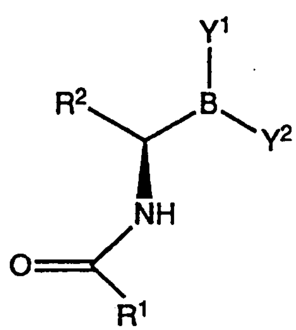


where R^2 is $X(CH_2)_3$-, and where R^1 is

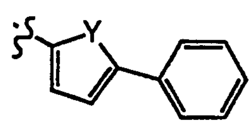


Ex	X	Y^1,Y^2	Phys Data
305	NHC(NH)NH_2	(+)-pinanediol	
306	SC(NH)NH_2	(+)-pinanediol	II
307	CH_2NH_2	(+)-pinanediol	
308	NHC(NH)NH_2	H,H	
309	SC(NH)NH_2	H,H	
310	CH_2NH_2	H,H	

TABLE 8

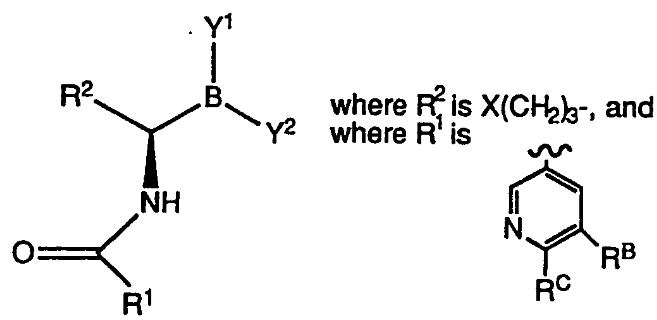


where R^2 is $X(CH_2)_3$-, and where R^1 is



Ex	X	Y	Y^1, Y^2	Phys Data
311	NHC(NH)NH$_2$	O	(+)-pinanediol	
312	SC(NH)NH$_2$	O	(+)-pinanediol	JJ
313	CH$_2$NH$_2$	O	(+)-pinanediol	
314	NHC(NH)NH$_2$	S	(+)-pinanediol	
315	SC(NH)NH$_2$	S	(+)-pinanediol	
316	CH$_2$NH$_2$	S	(+)-pinanediol	
317	NHC(NH)NH$_2$	O	H,H	
318	SC(NH)NH$_2$	O	H,H	
319	CH$_2$NH$_2$	O	H,H	
320	NHC(NH)NH$_2$	S	H,H	
321	SC(NH)NH$_2$	S	H,H	
322	CH$_2$NH$_2$	S	H,H	

TABLE 9

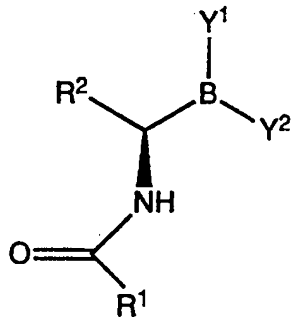


Ex	X	R^B	R^C	Y^1, Y^2	Phys Data
323	NHC(NH)NH$_2$	H	Ph	(+)-pinanediol	
324	NHC(NH)NH$_2$	OBn	H	(+)-pinanediol	
325	SC(NH)NH$_2$	Ph	H	(+)-pinanediol	KK
326	SC(NH)NH$_2$	H	OBn	(+)-pinanediol	LL
327	CH$_2$NH$_2$	H	Ph	(+)-pinanediol	
328	CH$_2$NH$_2$	OBn	H	(+)-pinanediol	
329	NHC(NH)NH$_2$	H	Ph	H,H	
330	NHC(NH)NH$_2$	OBn	H	H,H	
331	SC(NH)NH$_2$	H	Ph	H,H	

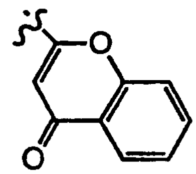
Ex	X	R^B	R^C	Y^1, Y^2	Phys Data
332	SC(NH)NH$_2$	OBn	H	H,H	

333	CH_2NH_2	H	Ph	H,H
334	CH_2NH_2	OBn	H	H,H

TABLE 10

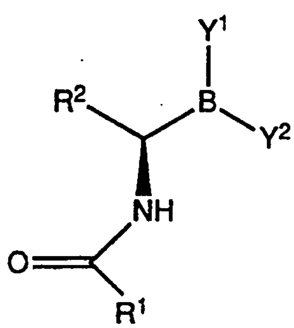


where R^2 is $X(CH_2)_3$-, and where R^1 is

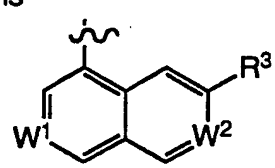


Ex	X	Y^1,Y^2	Phys Data
335	NHC(NH)NH_2	(+)-pinanediol	
336	SC(NH)NH_2	(+)-pinanediol	MM
337	CH_2NH_2	(+)-pinanediol	
338	NHC(NH)NH_2	H,H	
339	SC(NH)NH_2	H,H	
340	CH_2NH_2	H,H	

TABLE 11



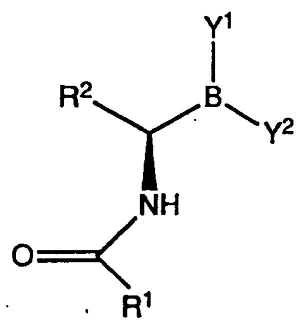
where R^2 is $X(CH_2)_3$-, and where R^1 is



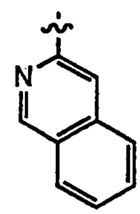
Ex	X	W^1	W^2	R^3	Y^1,Y^2	Phys

						Data
341	NHC(NH)NH_2	N	CH	H	(+)-pinanediol	
342	SC(NH)NH_2	N	CH	H	(+)-pinanediol	
343	CH_2NH_2	N	CH	H	(+)-pinanediol	
344	NHC(NH)NH_2	CH	N	Ph	(+)-pinanediol	
345	SC(NH)NH_2	CH	N	Ph	(+)-pinanediol	OO
346	CH_2NH_2	CH	N	Ph	(+)-pinanediol	
347	NHC(NH)NH_2	N	CH	H	H,H	
348	SC(NH)NH_2	N	CH	H	H,H	
349	CH_2NH_2	N	CH	H	H,H	
350	NHC(NH)NH_2	CH	N	Ph	H,H	
351	SC(NH)NH_2	CH	N	Ph	H,H	
352	CH_2NH_2	CH	N	Ph	H,H	

TABLE 12

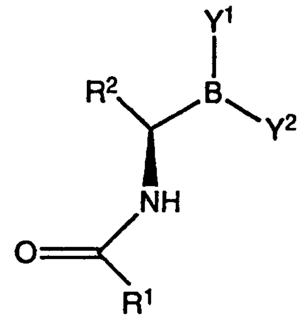


where R^2 is $X(CH_2)_3$-, and where R^1 is

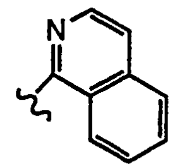


Ex	X	Y^1,Y^2	Phys Data
353	NHC(NH)NH_2	(+)-pinanediol	
354	SC(NH)NH_2	(+)-pinanediol	PP
355	CH_2NH_2	(+)-pinanediol	
356	NHC(NH)NH_2	H,H	
357	SC(NH)NH_2	H,H	
358	CH_2NH_2	H,H	

TABLE 13

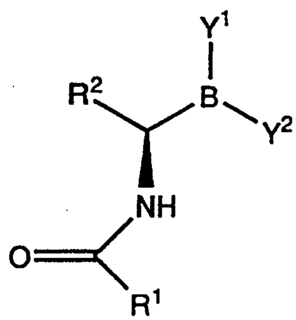


where R^2 is $X(CH_2)_3$-, and where R^1 is

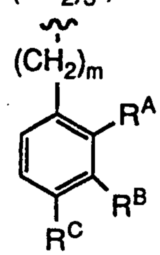


Ex	X	R^3	Y^1, Y^2	Phys Data
359	SC(NH)NH2	H	(+)-pinanediol	NN

TABLE 14



where R^2 is $X(CH_2)_3$-, and where R^1 is



Ex	X	m	R^A	R^B	R^C	Y^1, Y^2	Phys Data
	$SC(NH)NH_2$	2	H	$NHCO(CH_2)_2Ph$	H	(+)-pinanediol	RR
	$SC(NH)NH_2$	2	H	Ph	H	(+)-pinanediol	
	$SC(NH)NH_2$	2	H	OPh	Ph	(+)-pinanediol	
	$SC(NH)NH_2$	1	H	H	4-pyridyl	(+)-pinanediol	
	$NHC(NH)NH_2$	1	COPh	H	H	(+)-pinanediol	
	$NHC(NH)NH_2$	3	H	COPh	H	(+)-pinanediol	
	$NHC(NH)NH_2$	3	H	H	COPh	(+)-pinanediol	

Physical Data for Tables 1-14

A: MS $(M+H)^+$ = 489; ^1H NMR (400 MHz, $CDCl_3$, 60 °C) 9.48 (1H, bs), 8.10 (2 H, d, J = 8.1), 8.07 (1 H, bs), 7.75 (1 H, bs), 7.54 (2 H, d, J = 8.3), 7.48 (2 H, d, J = 7.0), 7.35 (3 H, m), 7.06 (4 H, bs), 4.19 (1 H, bd, J = 8.3), 3.1 (2 H, m), 2.84 (1 H, m), 2.29 (1 H, m), 2.12 (1 H, m), 1.96 (1 H, m), 1.75 (6 H, m), 1.47 (1 H, d, J = 10.2), 1.40 (3 H, s), 1.24 (3 H, s), 0.83 (3 H, s).

B: MS (DCI - NH_3), 505 $(M + H)^+$.

C: MS $(M+H)^+$ = 490.

D: MS $(M+H)^+$ = 506; ^1H NMR (300 MHz, $CDCl_3$) 8.15 (2 H, d, J = 8.4), 7.61 (2 H, d, J = 8.4), 7.52 (2 H, m), 7.38 (3 H, m), 6.47 (1 H, bs), 4.23 (1 H, dd, J = 6.6, 1.9), 3.24 (1 H, m), 3.14, (1 H, m), 2.96, (1 H, m), 2.32 (1 H, m), 2.15 (1 H, m), 1.99 (1 H, m), 1.78 (6 H, m), 1.48 (1 H, d, J = 10.1), 1.42 (3 H, s), 1.27 (3 H, s), 0.86 (3 H, s).

E: mp 145-150 °C.

F: MS (DCI - NH_3), 522 $(M + H)^+$.

G: HRMS (DCI - NH_3), Calc: 534.2597, Found: 534.2609.

H: HRMS (DCI - NH_3), Calc: 534.2597, Found: 534.2605.

I: HRMS (DCI - NH_3), Calc: 534.2597, Found: 534.2609.

J: $[a]_D$ = -14.85° (c = 0.606, MeOH); ^1H NMR (300 MHz, DMSO - d_6) 10.07 (br s, 1 H), 10.05 (br s, 1 H), 8.96 (4 H, br s), 8.08 (1 H, s), 7.71 (1 H, dd, J = 8.1,

1.1), 7.61 (1 H, d, J = 7.7), 7.30 - 7.50 (6 H, m), 5.18 (2 H, s), 4.08 (1 H, br d), 3.08 - 3.25 (2 H, m), 2.50 - 2.65 (1 H, m), 2.15 - 2.30 (1 H, m), 1.97 - 2.10 (1 H, m), 1.40 - 1.90 (8 H, m), 1.31 (3 H, s), 1.24 (3 H, s), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1734, 1646, 1578, 1550, 1440, 1222, 1058 cm^{-1}; MS (CI - NH_3), *m/e* (%) 537.2 (10.2, M + H - $H_2NCN)^+$), 429.0 (42.8), 277.0 (100); Anal. Calcd for $C_{30}H_{40}BBrN_4O_5S$: C, 54.64; H, 6.11; N, 8.50; B, 1.64. Found: C, 54.52; H, 6.16; N, 8.45; B, 1.60.

K: $[a]_D$ = -15.07° (c = 0.604, MeOH); ^1H NMR (300 MHz, DMSO - d_6) 9.98 (1 H, br s), 8.96 (4 H, br s), 7.93 (1 H, narrow m), 7.80 (1 H, app d), 7.64 (1 H, m), 7.56 (1 H, app t), 7.25 - 7.42 (5 H, m), 5.13 (2 H, s), 4.11 (1 H, dd, J = 8.3, 1.7), 3.30 (3 H, s), 3.10 - 3.25 (2 H, m), 2.57 - 2.68 (1 H, m), 2.15 - 2.30 (1 H, m), 1.97 - 2.10 (1 H, m), 1.48 - 1.90 (7 H, m), 1.44 (1 H, d, J = 9.9), 1.31 (3 H, s), 1.24 (3 H, s), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1710, 1647, 1159 cm^{-1}; MS (CI - NH_3), *m/e* (%) 593.2 (1.2, $(M + H)^+$), 568.3 (22, (M + NH_4 - $H_2NCN)^+$), 551.3 (100, (M + H - $H_2NCN)^+$); Anal. Calcd for $C_{31}H_{42}BBrN_4O_5S$: C, 55.29; H, 6.29; N, 8.32; B, 1.61. Found: C, 55.15; H, 6.21; N, 8.22; B, 1.47.

L: $[a]_D$ = -14.12° (c = 0.602, MeOH); ^1H NMR (300 MHz, DMSO - d_6) 10.09 (1 H, br s), 8.98 (4 H, br s), 7.90 (2 H, d, J = 8.3), 7.42 (2 H, d, J = 8.3), 4.06 (1 H, d, J = 7.0), 3.15 - 3.20 (2 H, m), 2.70 (2 H, q, J = 7.7), 2.54 (1 H, m), 2.18 - 2.28 (1 H, m), 1.98 - 2.08 (1 H, m), 1.44 - 1.84 (8 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 1.20 (3 H, t, J = 7.7), 0.84 (3 H, s); IR (KBr) 2600 - 3700 (br), 1646, 1614, 1598, 1570, 1500, 1123 cm^{-1}; MS (DCI - NH_3), *m/e* (%) 458 (100, (M

+ H)$^+$); Anal. Calcd for $C_{24}H_{37}BBrN_3O_3S$: C, 53.54; H, 6.93; N, 7.81; B, 2.01. Found: C, 53.75; H, 6.98; N, 7.74; B, 1.97.

M: $[a]_D$ = −14.21° (c = 0.556, MeOH); ^1H NMR (300 MHz, DMSO − d_6) 10.06 (1 H, br s), 8.95 (4 H, br s), 7.88 (2 H, d, J = 8.1), 7.40 (2 H, d, J = 8.1), 4.06 (1 H, dd, J = 1.7, 8.3), 3.14 − 3.17 (2 H, m), 2.65 (2 H, t, J = 7.5), 2.50 − 2.60 (1 H, m), 2.18 − 2.28 (1 H, m), 1.98 − 2.08 (1 H, m), 1.45 − 1.84 (10 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 0.89 (3 H, t, J = 7.3), 0.84 (3 H, s); IR (KBr) 2500 − 3700 (br), 1646, 1614, 1598, 1570, 1500, 1446, 1236, 1124, 1082 cm^{-1}; MS (CI − NH_3), *m/e* (%) 472.2 (13.5, (M + H)$^+$), 430.2 (100, (M + H − H_2NCN)$^+$), 278.0 (61.9); Anal. Calcd for $C_{25}H_{39}BBrN_3O_3S$: C, 54.36; H, 7.12; N, 7.61; B, 1.96. Found: C, 54.50; H, 7.18; N, 7.83; B, 1.73.

N: $[a]_D$ = −13.79° (c = 0.602, MeOH); ^1H NMR (300 MHz, DMSO − d_6) 10.03 (1 H, br s), 8.94 (4 H, br s), 7.89 (2 H, d, J = 8.3), 7.45 (2 H, d, J = 8.3), 4.06 (1 H, br d), 3.10 − 3.23 (2 H, m), 2.90 − 3.05 (1 H, m), 2.50 − 2.60 (1 H, m), 2.15 − 2.30 (1 H, m), 1.95 − 2.08 (1 H, m), 1.42 − 1.89 (8 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 1.23 (6 H, d, J = 7.0), 0.84 (3 H, s); IR (KBr) 2500 − 3700 (br), 1646, 1613, 1598, 1123 cm^{-1}; MS (DCI − NH_3), *m/e* (%) 472 (100, (M + H)$^+$), 430 (37, (M + H − H_2NCN)$^+$); Anal. Calcd for $C_{25}H_{39}BBrN_3O_3S$: C, 54.36; H, 7.12; N, 7.61; B, 1.96. Found: C, 54.64; H, 7.17; N, 7.50; B, 1.74.

O: $[a]_D$ = −13.19° (c = 0.364, MeOH); ^1H NMR (300 MHz, DMSO − d_6) 10.03 (1 H, br s), 8.93 (4 H, br s), 7.88 (2 H, d, J = 8.5), 7.40 (2 H, d, J = 8.5), 4.06 (1 H, br d, J = 6.6), 3.15 − 3.20 (2 H, m), 2.67 (2 H, t, J

= 7.7), 2.50 - 2.60 (1 H, m), 2.18 - 2.28 (1 H, m), 1.95 - 2.08 (1 H, m), 1.24 - 1.84 (10 H, m), 1.23 - 1.35 (2 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 0.90 (3 H, t, J = 7.3), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1614, 1598, 1500, 1123 cm^{-1}; MS (CI - NH_3), *m/e* (%) 486.2 (3.3, $(M + H)^+$), 444.2 (87.1, $(M + H - H_2NCN)^+$), 292.0 (100); Anal. Calcd for $C_{26}H_{41}BBrN_3O_3S$: C, 55.13; H, 7.30; N, 7.42; B, 1.91. Found: C, 54.99; H, 7.22; N, 7.29; B, 2.07.

P: $[a]_D$ = -12.71° (c = 0.598, MeOH); ^1H NMR (300 MHz, DMSO - d_6) 10.05 (1 H, br s), 8.95 (4 H, br s), 7.90 (2 H, d, J = 8.6), 7.59 (2 H, d, J = 8.6), 4.06 (1 H, br d), 3.10 - 3.23 (2 H, m), 2.50 - 2.62 (1 H, m), 2.16 - 2.30 (1 H, m), 1.96 - 2.08 (1 H, m), 1.42 - 1.90 (8 H, m), 1.31 (9 H, s), 1.30 (3 H, s), 1.24 (3 H, s), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1613, 1597, 1498, 1123 cm^{-1}; MS (DCI - NH_3), *m/e* (%) 486 (100, $(M + H)^+$), 444 (16, $(M + H - H_2NCN)^+$); Anal. Calcd for $C_{26}H_{41}BBrN_3O_3S$: C, 55.13; H, 7.30; N, 7.42; B, 1.91. Found: C, 55.09; H, 7.45; N, 7.40; B, 1.67.

Q: ^1H NMR (300 MHz, DMSO - d_6) δ10.06 (1 H, br s), 8.95 (4 H, br s), 7.88 (2 H, d, J = 8.5), 7.40 (2 H, d, J = 8.5), 4.06 (1 H, br d, J = 6.6), 3.10 - 3.23 (2 H, m), 2.66 (2 H, t, J = 7.7), 2.50 - 2.60 (1 H, m), 2.15 - 2.30 (1 H, m), 1.95 - 2.08 (1 H, m), 1.40 - 1.90 (10 H, m), 1.20 - 1.38 (12 H, m), 0.80 - 0.90 (6 H, m); IR (KBr) 2500 - 3700 (br), 1646, 1614, 1598, 1500, 1124 cm^{-1}; MS (DCI - NH_3), *m/e* (%) 514 (100, $(M + H)^+$), 472 (16, $(M + H - H_2NCN)^+$); Anal. Calcd for $C_{28}H_{45}BBrN_3O_3S$: C, 56.57; H, 7.63; N, 7.07; B, 1.82. Found: C, 56.19; H, 7.53; N, 6.97; B, 1.99.

R: $[a]_D = -11.70°$ (c = 0.530, MeOH); ^1H NMR (300 MHz, DMSO - d_6) d10.05 (1 H, br s), 8.83 - 9.13 (4 H, br d), 7.88 (2 H, d, J = 8.3), 7.43 (2 H, d, J = 8.3), 4.06 (1 H, br d), 3.05 - 3.25 (2 H, m), 2.45 - 2.67 (2 H, m), 2.13 - 2.30 (1 H, m), 1.94 - 2.10 (1 H, m), 1.30 - 1.90 (18 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1613, 1598, 1500, 1448, 1122 cm^{-1}; MS (DCI - NH_3), *m/e* (%) 512 (100, $(M + H)^+$), 470 (40, $(M + H - H_2NCN)^+$); Anal. Calcd for $C_{28}H_{43}BBrN_3O_3S$: C, 56.77; H, 7.32; N, 7.09; B, 1.82. Found: C, 56.49; H, 7.38; N, 6.96; B, 1.75.

S: HRMS (DCI - NH_3), Calc: 577.3019, Found: 577.3025.

T: $[a]_D = -8.31°$ (c = 0.614, MeOH); ^1H NMR (300 MHz, DMSO - d_6) d9.98 (1 H, br s), 8.95 (4 H, br s), 7.93 (2 H, d, J = 8.8), 7.11 (2 H, d, J = 8.8), 4.00 - 4.10 (3 H, m), 3.10 - 3.23 (2 H, m), 2.50 - 2.60 (1 H, m), 2.15 - 2.30 (1 H, m), 1.95 - 2.08 (1 H, m), 1.37 - 1.90 (12 H, m), 1.29 (3 H, s), 1.24 (3 H, s), 0.94 (3 H, t, J = 7.4), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1608, 1498, 1262, 1124 cm^{-1}; MS (DCI - NH_3), *m/e* (%) 502 (100, $(M + H)^+$), 460 (28, $(M + H - H_2NCN)^+$); Anal. Calcd for $C_{26}H_{41}BBrN_3O_4S$: C, 53.62; H, 7.10; N, 7.21; B, 1.86. Found: C, 53.61; H, 7.09; N, 7.20; B, 1.78.

U: HRMS (DCI - NH_3), Calc: 513.2707, Found: 513.2702.

V: HRMS (DCI - NH_3), Calc: 555.3165, Found: 555.3176.
W: HRMS (DCI - NH_3), Calc: 579.2812, Found: 579.2801.

X: HRMS (DCI - NH_3), Calc: 450.2962, Found: 450.2958.

Y: HRMS (DCI - NH_3), Calc: 640.3016, Found: 640.3022.

Z: $[a]_D$ = -8.80° (c = 0.602, MeOH); ^1H NMR (300 MHz, DMSO - d_6) 10.03 (1 H, br s), 9.25 (1 H, br s), 8.96 (4 H, br s), 7.92 (1 H, d, J = 1.5), 7.72 (1 H, dd, J = 8.1, 1.5), 7.25 - 7.50 (6 H, m), 5.17 (2 H, s), 4.08 (1 H, dd, J = 8.1, 1.5), 3.08 - 3.27 (2 H, m), 2.65 (2 H, br t), 2.50 - 2.60 (1 H, m), 2.15 - 2.30 (1 H, m), 1.95 - 2.08 (1 H, m), 1.40 - 1.90 (10 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 1.15 - 1.38 (2 H, m, buried underneath methyl absorptions), 0.77 - 0.95 (6 H, m); IR (KBr) 2500 - 3700 (br), 1704, 1646, 1572, 1539, 1453, 1234, 1123, 1056 cm^{-1}; MS (CI - NH_3), *m/e* (%) 593.2 (1.3, $(M + H - H_2NCN)^+$), 485.2 (42.7), 333.0 (100); Anal. Calcd for $C_{34}H_{48}BBrN_4O_5S$: C, 57.07; H, 6.76; N, 7.83; B, 1.51. Found: C, 57.17; H, 6.84; N, 7.76; B, 1.41.

AA: ^1H NMR (300 MHz, DMSO - d_6) §9.98 (1 H, br s), 8.98 (4 H, br s), 7.77 - 7.92 (2 H, m), 7.08 - 7.55 (6 H, m), 4.90 - 5.30 (2 H, m), 4.09 (1 H, br d), 3.04 - 3.35 (5 H, m), 2.35 - 2.65 (3 H, m), 2.15 - 2.30 (1 H, m), 1.97- 2.10 (1 H, m), 1.37- 1.93 (10 H, m), 1.31 (3 H, s), 1.24 (3 H, s), 1.10 - 1.37 (2 H, m, buried underneath methyl absorptions), 0.72 - 0.93 (6 H, m); MS (CI - NH_3), *m/e* (%) 649.4 (1.9, $(M + H)^+$), 624.4 (31, $(M + NH_4 - H_2NCN)^+$), 607.2 (100, $(M + H - H_2NCN)^+$), 455.0 (39), 444.0 (29.8); Anal. Calcd for $C_{35}H_{50}BBrN_4O_5S$: C, 57.62; H, 6.91; N, 7.68; B, 1.48. Found:
C, 57.37; H, 6.86; N, 7.64; B, 1.40.

BB: HRMS (DCI - NH_3), Calc: 520.2805, Found: 520.2796.

CC: HRMS (DCI - NH_3), Calc: 560.2390, Found: 560.2407.

DD: HRMS (DCI - NH_3), Calc: 596.2060, Found: 596.2055.

EE: HRMS (DCI - NH_3), Calc: 546.2597, Found: 546.2604.

FF: HRMS (DCI - NH_3), Calc: 534.2597, Found: 534.2609.

GG: HRMS (DCI - NH_3), Calc: 532.2441, Found: 532.2445.

HH: HRMS (DCI - NH_3), Calc: 532.2441, Found: 532.2452.

II: HRMS (DCI - NH_3), Calc: 480.2493, Found: 480.2492.

JJ: HRMS (DCI - NH_3), Calc: 496.2441, Found: 496.2449.

KK: HRMS (DCI - NH_3), Calc: 507.2601, Found: 507.2592.

LL: HRMS (DCI - NH_3), Calc: 537.2667, Found: 537.2685.

MM: HRMS (DCI - NH_3), Calc: 498.2233, Found: 498.2231.

NN: HRMS (DCI - NH_3), Calc: 481.2445, Found: 481.2442.

OO: HRMS (DCI - NH_3), Calc: 557.2758, Found: 557.2754.

PP: HRMS (DCI - NH_3), Calc: 5481.2445, Found: 481.2440.

QQ: HRMS (NH_3) - CI/DEP), Calc: 503.3193, Found: 503.3199.

RR: HRMS (DCI-NH_3), Calc: 605.333; Found: 605.3325.

Utility

The compounds of formula (I) are useful as inhibitors of trypsin-like enzymes, notably human thrombin, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological

reactions catalyzed by the aforesaid enzymes such as blood coagulation and inflammation.

As an illustration of the above, the biological activity of compounds of the present invention is demonstrated by their *in vitro* inhibition of synthetic substrate hydrolysis by human thrombin S-2238 Chromogenic Assay (IC_{50}). The synthetic substrate H-*D*-Phe-Pip-Arg-pNA (S-2238, Kabi) is cleaved by thrombin, liberating the *p*-nitroanalide group which absorbs light at 405 nm. Enzyme activity is measured in both the presence and absence of inhibitor. A decrease in absorbance at 405 nm in the presence of inhibitor is indicative of thrombin inhibition.

A mixture of 10 μL human thrombin (Enzyme Research Laboratories, Inc.) at an activity of approximately 7 units/mL, 10 μL of the inhibitor (normally at a concentration of 10^{-3} *M* or less), and 160 μL buffer (0.15 *M* NaCl, 10 m*M* HEPES, 10 m*M* Tris, 1 g/L PEG 8,000, pH 7.4) are incubated for 10 minutes at room temperature. To this mixture is added 20 μL of the synthetic substrate S-2238 at a concentration of 1 m*M* and the reaction allowed to occur for 10 minutes, after which absorbance at 405 nm is determined.

Using the methodology described above, representative compounds of this invention were evaluated and found to exhibit an IC_{50} of less than 1 m*M*, thereby confirming the utility of the compounds of the invention as effective thrombin inhibitors.

Since the compounds of formula (I) have anti-thrombogenic properties, they may be employed when an anti-thrombogenic agent is indicated, such as for control of the coagulation or the fibrinolysis system in mammals or they may be added to blood for the purpose of preventing coagulation or the blood due to

contact with blood collecting or distribution containers, tubing or apparatus.

Generally, these compounds may be administered orally or parenterally to a host to obtain an anti-thrombogenic effect. The dosage of the active compound depends on the mammalian species, body weight, age, and mode of administration as will be obvious to one skilled in the art. In the case of large mammals such as humans, the compounds may be administered alone or in combination with pharmaceutical carriers or diluents at a dose of from 0.02 to 15 mg/Kg to obtain the anti-thrombogenic effect, and may be given as a single dose or in divided doses or as a sustained release formulation.

Pharmaceutical carriers or diluents are well known and include sugars, starches and water, which may be used to make tablets, capsules, injectable solutions or the like which can serve as suitable dosage forms for administration of the compounds of this invention. Remington's Pharmaceutical Sciences, A. Osol, is a standard reference text which discloses suitable pharmaceutical carriers and dosage forms. The disclosure of this text is hereby incorporated by reference for a more complete teaching of suitable dosage forms for administration of the compounds of this invention.

WHAT IS CLAIMED IS:

1. A compound of formula (I)

$$R^1\text{-}Z\text{-}CCHR^2\text{-}BY^1Y^2$$

(I)

wherein

Y^1 and Y^2 are independently

a) -OH

b) -F,

c) - NR^3R^4, or

d) C1-C8- alkoxy;

Y^1 and Y^2 when taken together can form

a) a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and,optionally, a heteroatom which can be N, S, or O,

b) a divalent cyclic boro amide where said chain or ring contains from 2 t 20 carbon atoms,

c) a cyclic boro amide-ester where said chain or ring contains from 2 to 20 carbon atoms;

Z is

a) $-(CH_2)_mCONR^8-$,

b) $-(CH_2)_mCSNR^8-$,

c) $-(CH_2)_mSO_2NR^8-$,

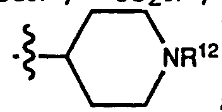
d) $-(CH_2)_mCO_2-$,

e) $-(CH_2)_mC(S)O-$, or

f) $-(CH_2)_mSO_2O-$;

R^1 is

a) $-(CH_2)_p$-aryl, wherein aryl is phenyl, naphthyl or biphenyl substituted with one, two or three substituents selected from the group consisting of halo (F, Cl, Br, I), CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl,

C2--C10-alkynyl, $-R^8$, $-OR^8$, methylenedioxy, $-NO_2$, $-CF_3$, $-S(O)_rR^7$, NR^8R^9, $-COR^8$, $-CO_2R^8$, $-CONR^8R^9$, NR^8COR^9, $NR^8CO_2R^9$,  ;

b) heteroaryl, wherein heteroaryl is an unsubstituted or monosubstituted or disubstituted

i) 5- or 6-membered aromatic ring, which contains from 1 to 3 heteroatoms selected from the group consisting of O, N, and S,

ii) quinolinyl,

iii) isoquinolinyl,

iv) benzopyranyl,

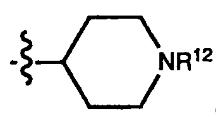
v) benzothiophenyl,

vi) benzofuranyl,

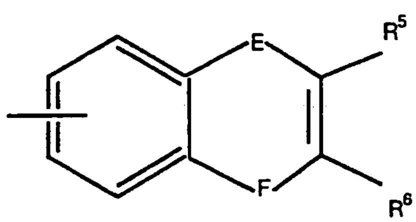
vii) 5,6,7,8-tetrahydroquinolinyl

viii) 5,6,7,8-tetrahydroisoquinolinyl

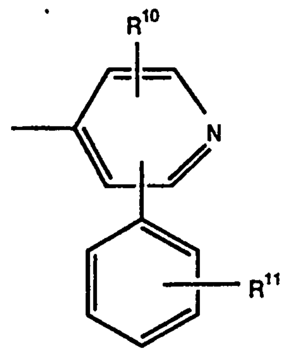
and wherein the subtitutents are members selected from the group consisting of halo (F, Cl, Br, I, -CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, $-R^8$, OR^8, NO_2, $-CF_3$, $-S(O)_rR^7$, NR^8R^9, $-COR^8$, $-CONR^8R^9$, NR^8COR^9, $NR^8CO_2R^9$,



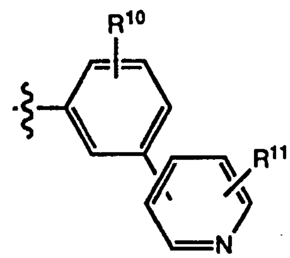
;

c) 

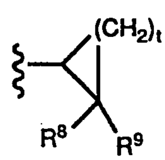
d)



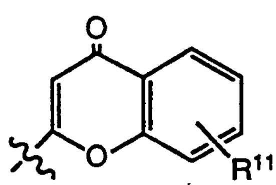
e)



f)



g)



R^2 is

a) $-(CH_2)_n-NHC(NH)NH_2$,

b) $-(CH_2)_n-NHC(NH)NHCOCH_3$,

c) $-(CH_2)_n-SC(NH)NH_2$,

e) $-(CH_2)_n-SC(NH)_2$, or

f) $-(CH)_n-NH$(2-pyridyl);

R^3 is H, phenyl or C1-C4-alkyl;

R^4 is H, or phenylsulfonyl;

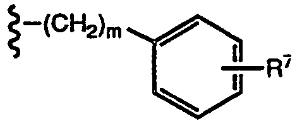
R^5 and R^6 are hydrogen or when taken together form a six membered aromatic ring optionally substituted with one, two or three substituents selected from the group consisting of halo (F, Cl, Br, I), -CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, $-OR^8$, $-NO_2$, $-CF_3$, $-S(O)_rR^7$, $-NR^8R^9$, $-COR^8$, $-COR_2R^8$, $-CONR^8R^9$, phenyl, benzyl, phenylethyl;

R^7 is

a) phenyl,
b) C1-C4-alkyl,
c) C1-C4-alkoxy, or
d) $-CF_3$;

R^8 and R^9 are independently

a) H,
b)



c) C3-C7-Cycloalkyl,
d) C1-C8-alkyl;

R^{10} and R^{11} are independently

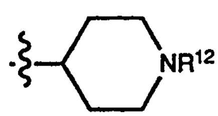
a) halo (F, Cl,Br, I),
b) -CN,
c) C1-C10-alkyl,
d) C3-C8-cycloalkyl,
e) C2-C10-alkenyl,
f) C2-C10-alkynyl,
g) $-OR^8$,
h) NO_2,
i) $-CF_3$,
j) $-S(O)_rR^7$,
k) $-NR^8R^9$,
l) $-COR^9$,
m) $-CO_2R^8$, or
n) $-CONR^8R^9$;

R^{12} is

a) H,
b) C1-C4-alkyl,
c) phenyl
d) benzyl,
e) $-COR^7$
f) $-SO_2R^7$

m is 0 to 6;
n is 3 or 4;
p is 0 to 2;
r is 0 to 2;
t is 1 to 5
E is -CO-, $-SO_2-$,$-CH_2-$ or a single bond,
F is -CO-, and
pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein:
R1 is phenyl containing 1-3 substituents selected from the series halo (F, CL, Br, I), C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, $-R^8$, $-OR^8$, $-NO_2$, $-CF_3$, $-S(O)_rR^7$, $-NR^8R^9$, $-COR^8$, $-CO_2R^8$, $CONR^8R^9$, NR^8COR^9, and



; and

R_2 is

a) $-(CH_2)_3-NHC(NH)NH_2$, or
b) $-(CH_2)_3-SC(NH)NH_2$.

3. A compound of Claim 2 wherein Z is $-(CH_2)_mCONR^8-$.

4. A compound of Claim 3 selected from the group consisting of
N^1-(4-phenylbenzoyl)-(R)-boroarganine, hydrochloride,

N^1-(3-phenoxybenzoyl)-(R)-boroarganine, hydrochloride,
N^1-(1-fluorenonyl)-(R)-boroarginine, hydrochloride,
N^1-(4-[butyl]benzoyl)-(R)-boroarginine, hydrochloride,
N^1-(2-benzoylbenzoyl)-R-boroarginine, hydrochloride,
N^1-(5-phenyl-2-furol)-R-boroarginine, hydrochloride,
N^1-(3-[N-benzyloxycarbonyl-N-methylamino]-4-[1-butyl]-benzoyl)-(R)-boroarginine, hydrochloride,
N^1-(2-phenyl-4-isoquinolyl)-(R)-boroarginine, hydrochloride,
N^1-(4-cyclohexylbenzoyl)-(R)-boroarginine, hydrochloride
N1-(2-methyl-4-phenylbenzoyl)-(R)-boroarginine, hydrochloride, or

5. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a therapeutically effective amount of a compound of any one of claims 1 through 4.

6. A method of treating a physiological disorder in a warm blooded animal catalyzed by trypsin-like enzymes comprising administering to an animal in need of such treatment an effective amount of a compound of any one of claims 1 through 4.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 94/02965

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07F5/02 A61K31/69

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 471 651 (SANDOZ LTD/SANDOZ-PATENT-GMBH/SANDOZ-ERFINDUNGEN) 19 February 1992 cited in the application see the whole document ---	1-6
A	WO,A,92 07869 (KAKKAR, V.V. ET AL.) 14 May 1992 see the whole document ---	1-6
A	EP,A,0 293 881 (E.I. DU PONT DE NEMOURS AND COMPANY) 7 December 1988 cited in the application see the whole document -----	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 1994	14. 06. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Rinkel, L

INTERNATIONAL SEARCH REPORT

International application No.

PCT/ US 94/ 02965

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claim 6 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition."

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 94/02965

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0471651	19-02-92	AU-B-	643312	11-11-93
		AU-A-	8179291	20-02-92
		CA-A-	2048953	14-02-92
		JP-A-	4330094	18-11-92
		US-A-	5288707	22-02-94
WO-A-9207869	14-05-92	AU-B-	636521	29-04-93
		AU-A-	8900791	26-05-92
		EP-A-	0509080	21-10-92
		JP-T-	5504775	22-07-93
EP-A-0293881	07-12-88	US-A-	5187157	16-02-93
		AU-B-	623592	21-05-92
		AU-A-	1733288	08-12-88
		CA-A-	1328332	05-04-94
		DE-A-	3878991	15-04-93
		JP-A-	1063583	09-03-89
		US-A-	5242904	07-09-93
		US-A-	5250720	05-10-93